BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 14 1960

DISINFECTION OF THE HANDS OF SURGEONS AND NURSES

BY

E. J. L. LOWBURY, M.A., D.M.

AND

H. A. LILLY, F.I.M.L.T.

Medical Research Council Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital

The hands of the nurse and the surgeon are undoubtedly two of the chief vectors of hospital infection. They often carry pathogenic organisms, in particular *Staphylococcus aureus*, which may be present in large numbers. Price (1938) has shown that scrubbing with soap and water for six minutes will reduce the numbers of bacteria on the hands by only about 50%. Devenish and Miles (1939) and others have found that about 30% of the rubber gloves worn at operations become punctured without the surgeon's knowledge, and bacteria can readily escape through the small holes which appear. Though these facts about hand scrubbing and gloves are quite well known, additional safeguards against manual contamination of wounds are not often used by surgeons; nurses, for their part, are generally not expected to do anything more to control their hand flora than washing with soap and water after certain ward duties.

Various antiseptics have been found to reduce the numbers of bacteria on the hands. Hexachlorophane soap (Traub, Newhall, and Fuller, 1944; Seastone, 1947) and "phisohex" (Hufnagel, Walter, and Howard, 1948) have been used for some years by surgeons in the United States, and a British paper in support of the latter has recently appeared (Smylie, Webster, and Bruce, 1959). Price (1951) has stressed the limitations of hexachlorophane soap when used irregularly, and finds that a conventional scrub with soap and water followed by three minutes' rinse in 70% alcohol before putting on gloves is more effective. The regular use of a hand cream containing chlorhexidine has been found to reduce the skin flora (Murray and Calman, 1955; Laurell, 1959), and its use by nurses in surgical and obstetric wards has been associated with some reduction in the incidence of cross-infection (Cook, Parrish, and Shooter, 1958; Gillespie, Simpson, and Tozer, 1958).

In this paper we describe experiments on the relative merits of several pre-operative antiseptic applications to the surgeon's hands, with particular reference to the numbers of bacteria emerging through holes in gloves. We also describe a study on the routine use of hexachlorophane soap and some other methods by nurses working in accident and burns wards.

The Surgeon's Hands

The efficiency of various antiseptic treatments of the surgeon's hands was measured by the numbers of bacteria that escape through holes in gloves after one hour's operation, and by the numbers of bacteria left inside the gloves after their removal.

Materials and Methods

The "surgeons" in this experiment were five members of the laboratory staff, and they wore rubber gloves for one hour (and in one series for three hours) while working at the bench. Before the experiment small pinholes were made with a No. 1 hypodermic needle at the tips of all fingers of one glove in each pair. The gloves were autoclaved at 10 lb. (4.5 kg.) for 20 minutes. Before putting on the gloves the operator cleansed his hands in one of the following ways: (1) a quick "social" wash with soap and water; (2) five minutes' scrub with a bristle brush and bar soap under running warm water; (3) five minutes' scrub, as described, followed by (*a*) three minutes' rinse in 70% alcohol (by weight), or (*b*) three minutes' rinse in 70% alcohol containing 0.5% chlorhexidine digluconate, or (*c*) a quick mopping of the hands with a swab soaked in industrial spirit (as used by some surgeons to dry the skin more quickly), or (*d*) the use of a glove powder containing 5 mg. of neomycin sulphate and 5 mg. of bacitracin per gramme of powder; (4) the use of 2% hexachlorophane soap ("medisoap") for all ablutions and baths during the week before the experiment, and for the five minutes' scrub in the experiment; and (5) the use of "phisohex" in place of hexachlorophane soap as described under (4), except that the pre-operative scrub was for two minutes only. Phisohex is a combination of 3% hexachlorophane with a cream containing an anionic detergent, "phisoderm" (Hufnagel *et al.*, 1948).

Each operator made an experiment with each antiseptic treatment. The experiment on antiseptic treatment was always made approximately one week after a control experiment with five minutes' scrub only, so that the consequences of possible cumulative action of antiseptics should be avoided. No experiment was made on any subject for a period of four weeks after the tests with antiseptics, so that the skin flora should be completely restored before the next control experiment.

Bacteriological sampling was carried out as follows. After the "operation" the gloved hands were washed with ordinary soap under a running tap, and dried on

a sterile towel. The tips of the fingers of both hands were then inserted into short flat-bottomed tubes (3 in. by 1 in.; 7.5 by 2.5 cm.), containing small glass beads and 5 ml. of sterile Ringer's solution with a neutralizer (see below). Each finger was rubbed for three minutes against the beads; the corresponding fingers of right and left hands were taken in pairs to minimize differences in the sampling of the two sides. The gloves were then removed. 100 ml. of Ringer's solution, with neutralizer when required, were pipetted into the gloves, which were shaken in a standard way; 5-ml. amounts of the sampling fluid were then transferred from the gloves to sterile tubes.

Pour plates were prepared by mixing 1-ml. amounts of 10^0 and 10^{-1} dilutions of all the sampling fluids with nutrient agar containing an appropriate neutralizer—for hexachlorophane and phisohex, 1% "Tween 80" (Lawrence and Erlandson, 1953; Smylie *et al.*, 1959), for chlorhexidine, 1% "lubrol W" and 0.5% lecithin (Gillespie *et al.*, 1958). For neomycin and bacitracin no neutralizer was available, but in four of the five experiments with these antibiotics we tested for the transfer of inhibitory concentrations by inoculating tubes of the sampling fluid and the pour plates with 0.02-ml. drops of a 10^{-4} dilution of a broth culture of highly sensitive organisms (*Staph. aureus*); similar inocula were made in control tubes of Ringer's solution and on control plates of nutrient agar. There was no consistent difference in the numbers of colonies growing from the sampling and the control fluids and culture media, and it was concluded that inhibitory levels of neomycin and bacitracin were not being transferred in these tests.

The plates were incubated at 37° C. for about 42 hours and colonies were counted, when possible, on the plates both from 10^0 and from 10^{-1} inocula, or alternatively on the one showing the optimum density of growth.

Results

Table I gives an example of the bacterial counts obtained from four punctured and four intact glove fingers in one experiment, including results from the control test (five minutes' scrub) and for the treatment test (scrub followed by chlorhexidine-alcohol rinse). For the assessment of the numbers of bacteria emerging through holes we subtracted the counts of bacteria rubbed on the fingers of intact gloves from the counts of bacteria rubbed off the corresponding punctured glove fingers. The results are expressed as counts (per ml.) of viable bacteria emerging through glove holes.

Table II shows the effect of five minutes' surgical scrub with ordinary bar soap. The mean estimated count of bacteria emerging through glove holes and the mean count of bacteria remaining in the glove were

TABLE I.—*Example of Experiment on Emergence of Bacteria Through Glove Holes*

Treatment of Hands	Viable Counts per ml. of Washings from Fingers of							
	Left Hand (Holes in Gloves)				Right Hand (No Holes)			
	2	3	4	5	2	3	4	5
5 minutes' scrub	242	420	130	210	4	1	3	3
5 minutes' scrub + 3 minutes' rinse in 70% alcohol with chlorhexidine 0·5% ..	14	5	4	4	10	2	9	4

TABLE II.—*Effect of Pre-operative Scrub and Length of Operation on Flora of Hands*

Treatment of Hands	Gloves Worn For	Mean Viable Counts per ml. Glove Washings		Mean Estimated Counts per ml. Washings, of Bacteria Emerging through Holes in Gloves	
		Bacteria per ml.*	No. of Samples	Bacteria per ml.*	No. of Samples
Social wash	1 hour	133·9 ± 24	10	163·8 ± 5·6	20
5 minutes' scrub ..	1 ,,	62·5 ± 18	10	81·0 ± 12	19
,, ,,	3 hours	128·2 ± 38	10	69·9 ± 4·7	20

* Here and in Tables III and V ± indicates the standard error of the mean.

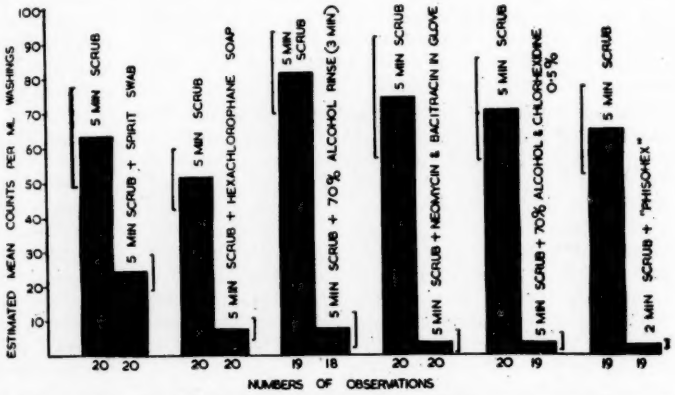


FIG. 1.—Effect of various methods of hand disinfection on the emergence of bacteria through holes in rubber gloves. For each method the mean count after use of an antiseptic (column on right) is compared with the mean count in a control experiment (column on left). Brackets indicate the standard error of the mean.

TABLE III.—*Effect of Antiseptic Treatment on Flora of Hands*

Antiseptic Treatment of Hands	Mean Bacterial Counts per ml. Glove Washings After				Mean Estimated Counts, per ml. Washings, of Bacteria Emerging through Holes in Glove After			
	Scrubbing Up + Antiseptic Treatment	No. of Samples	Scrubbing Up Only (Controls)	No. of Samples	Scrubbing Up + Antiseptic Treatment	No. of Samples	Scrubbing Up Only (Controls)	No. of Samples
Neomycin and bacitracin in glove powder	0·6 ± 1·1	10	332·5 ± 120	10	3·7 ± 3·1	20	73·6 ± 17	20
70% alcohol rinse (3 minutes) ..	3·0 ± 0·7	10	62·5 ± 18	10	7·5 ± 5·4	18	81·0 ± 12	19
70% alcohol with 0·5% chlorhexidine rinse (3 minutes)	3·1 ± 0·7	10	151 ± 48	10	3·25 ± 2·1	19	69·9 ± 14	20
Spirit swab	79·5 ± 36	10	392 ± 140	10	24·2 ± 4·1	20	63·2 ± 14	20
Hexachlorophane soap (for scrub and previous week)	14·9 ± 6	10	169 ± 66	10	7·3 ± 2·8	20	51·2 ± 8·7	20
Phisohex (for scrub and previous week)	1·9 ± 0·7	10	127 ± 39	10	2·7 ± 1·3	19	63·8 ± 13	19
Total (controls)	—	—	206 ± 38	60	—	—	67·0 ± 4·5	118

about half of the means found in such tests after a social wash. Table II also shows that larger numbers of bacteria were obtained from the glove washings (though not through holes in the gloves) when the operations lasted three hours instead of one hour.

Table III shows the mean viable counts from control and treatment series, including both the glove washings and the estimated numbers of bacteria emerging through holes in gloves; a summary of the latter is shown in Fig. 1. The relative merits of the different methods of hand disinfection were found to be approximately the same by both methods, except in the case of neomycin and bacitracin, which showed a larger effect in the tests of glove washings. Each method of disinfection, except the use of a spirit swab, showed a striking suppressive effect on the hand flora when compared with its own control or with the mean of all the control results. Neomycin and bacitracin in glove powder were outstandingly effective, especially on the glove washings. Phisohex was also outstanding, and more effective than hexachlorophane soap. Chlorhexidine with alcohol was excellent, and somewhat better than alcohol alone in both forms of test. There was considerable variation in the mean control counts in different series of experiments. The highest counts of bacteria in glove washings were obtained during periods of hot weather, and were associated with profuse sweating; except in the experiments on one subject, there was no corresponding association of hot weather with high counts of bacteria emerging through holes in gloves.

Bacteria in Glove Washings from Real Operations

In a series of clean surgical operations, 20 gloves were taken from surgeons after use, and glove washings were examined by the method described above. The operations were of varying duration, some shorter and some longer than one hour; the gloves were sent to the laboratory when pinholes had been detected during or after operation by the method of Penikett and Gorrill (1958), and a proportion of the gloves were in use for only part of the operation. Fifteen of the gloves were from one surgeon, who had scrubbed up for five minutes, using ordinary soap and swabbing with a spirit swab before putting on gloves; approximately the same method was used by the other surgeons. The mean count of bacteria per ml. of glove washings was 37.4 ± 5.2. This was lower than the mean count from mock operations with the same pre-operative hand treatment, but the data for the latter were obtained during a period of hot weather when the bacterial counts from controls were exceptionally high (see Table III): the samples from the surgeons' hands were taken in winter and early spring.

The Nurses' Hands

We set out to find if the numbers of bacteria, and especially of staphylococci, on the hands of nurses could be reduced by regular use of hexachlorophane soap or by chlorhexidine cream, or by the combination of these methods.

Materials and Methods

Eighteen nurses (six from each of two accident wards and six from the burns unit) were chosen for the experiment.

For periods of a fornight each nurse used a particular form of hand hygiene; these were, in order of use: (1) ordinary bar soap; (2) hexachlorophane soap while the nurse was on duty in the ward (burns unit only); (3) the use of hexachlorophane soap for all ablutions and baths, in hospital and off duty; (4) hexachlorophane soap for all ablutions and baths and 1% chlorhexidine ("hibitane") hand cream applied after washing three or four times a day; (5) ordinary bar soap, and chlorhexidine hand cream applied three or four times a day after washing in the ward; and, finally, (6) ordinary bar soap again. Ordinary cotton towels were used in the ward, and no details of routine were changed. If a nurse was absent for some days she was required to be on duty in the ward for about a week before re-entering the experiment, so that her hands could again acquire a representative sample of the ward flora.

At weekly intervals—twice during each treatment period of the study—the nurses were asked to wash their hands "socially" with soap and water, dry them on a clean cotton towel, and then provide a sample of standard hand washings in sterile physiological saline containing 5% nutrient broth. These washings were collected as follows. Broth-saline (100 ml.) was poured into a stainless-steel basin. The nurse then moistened both surfaces of both hands with the broth-saline solution, and rubbed the hands together 20 times (with single strokes) in each of the following ways: (1) palm to palm, (2) right palm over left dorsum, (3) left palm over right dorsum, and (4) with fingers interlocking. The hands were thoroughly rinsed after each of these manœuvres. Nose swabs were taken from nurses in the accident wards. Approximately 10 ml. of washings from each nurse was transferred to a screw-cap bottle and taken to the laboratory.

Measured inocula (0.5 ml. of 10^0 and 0.04 ml. of 10^{-1} dilution) of these hand washings were spread with a sterile glass spreader on plates of phenolphthalein phosphate agar (Barber and Kuper, 1951) containing the appropriate antiseptic neutralizer (see above). The plates were incubated for 48 hours at 37° C. and counts of total organisms were made. Presumptive *Staph. aureus* colonies were counted immediately after exposure of the plate over strong ammonia. Nose swabs from the nurses were inoculated on horse-blood agar and incubated at 37° C. for 24 hours; colonies resembling staphylococci were tested by a tube coagulase test. Coagulase- and phosphatase-positive staphylococci (one colony per plate) were phage-typed and tested for sensitivity to penicillin, tetracycline, erythromycin, chloramphenicol, and novobiocin by a ditch-plate method with sensitive controls.

Results

Figs. 2 and 3 show the effect of the use of hexachlorophane soap in the accident wards (C and D) and in the burns unit. The counts of total organisms and of presumptive *Staph. aureus* were consistently lower in the samples taken when the nurses were using hexachlorophane soap. The differences were small compared with those observed in the study on gloved hands. This may be due to differences in the techniques (and purposes) of the two experiments, and perhaps also to the greater likelihood of repeated contamination of hands among members of the nursing staff. Though the reduction in the numbers of staphylococci on hands of nurses using hexachlorophane soap might seem

disappointing, the frequency of contamination (see Table IV) was significantly reduced (by about 50%).

Hexachlorophane used by nurses while on duty only and chlorhexidine cream applied three or four times a day were of dubious value (see Table V). The use of chlorhexidine cream in this way by nurses who were using hexachlorophane soap for all ablutions and baths did not lead to any further reduction in the mean numbers of bacteria in hand washings. There was some further reduction in the hand flora during the use of the combination in the burns unit, but when the findings in all the wards were taken into account there were somewhat larger numbers of bacteria isolated from hands treated by the combination of hexachlorophane and chlorhexidine than from those treated with hexachlorophane soap alone.

TABLE IV.—*Use of Hexachlorophane Soap and Isolation of Staph. aureus from Nurses' Hands in Three Wards*

Soap Used	Wards	*Staph. aureus* in Hand Washings			
		Present	Samples	% +	Significance Tests
Ordinary	C, D, and burns	48	56	86	C, D, and burns: $\chi^2=15{\cdot}8$, $P<0{\cdot}001$
	C and D	31	39	79	
Hexachlorophane	C, D, and burns	20	43	46	C and D wards: $\chi^2=11{\cdot}3$, $P<0{\cdot}001$
	C and D	11	30	33	

TABLE V.—*Effect of Various Forms of Disinfection on Hand Flora of Nurses in Accident and Burns Wards*

Treatment of Hands	All Colonies		*Staph. aureus*	
	Mean Counts per 0·1-ml. Washings	No. of Samples	Mean Counts per 1-ml. Washings	No. of Samples
Bar soap 1st series	504 ± 72	35	72·1 ± 13	36
Bar soap 2nd ,,	635 ± 74	27	127 ± 52	27
Hexachlorophane soap (exclusive use)	186 ± 27	42	29·7 ± 8·5	42
Hexachlorophane soap* (in ward only)	317 ± 31	12	162 ± 56	12
Hexachlorophane soap (exclusive use) and chlorhexidine cream (3 or 4 times a day)	202 ± 51	36	42·7 ± 48	36
Chlorhexidine cream (3 or 4 times a day)	352 ± 67	36	57·6 ± 14	36

* In burns wards only.

Tests for Mutual Inactivation of Chlorhexidine and Hexachlorophane

The minimal inhibitory concentration (M.I.C.) of hexachlorophane and of chlorhexidine against four strains of *Staph. aureus* was tested by a tube dilution test. Further tests were then carried out with mixtures of the antiseptics in the proportions of their M.I.C.s; in the mixture, the M.I.C.s of hexachlorophane and of chlorhexidine were reduced in respect of one of the strains, and unaltered in respect of the others. It was inferred from this experiment that there is no mutual inactivation of these antiseptics.

Bacterial Flora of Nurses' Hands

All of the 18 nurses who took part in this study carried *Staph. aureus* on their hands in at least a proportion of the samples taken during the period when ordinary soap was in use. Sensitivity tests and phage-typing showed that these strains were typical of the ward environment. For example, 14 of the 17 staphylococci isolated in the burns unit, 14 of the 18 isolated in ward C, and 15 of the 16 strains from ward D were resistant to penicillin. Five of the strains from the burns unit were also resistant to erythromycin and novobiocin, antibiotics which were sometimes used in the treatment of burns patients; in the other wards, however, where these antibiotics were hardly ever used, all the staphylococci from the nurses' hands were sensitive both to erythromycin and to novobiocin.

Some nurses yielded consistently high or low counts of bacteria; some tended to keep the same type of staphylococcus for long periods, others to acquire new types. The hands were more often found to carry staphylococci than noses (only one of the six nurses in the burns unit yielded *Staph. aureus* from a nose swab). Coliform bacilli of types commonly present in burns were sometimes found in large numbers on the hands of nurses in the burns unit; these organisms are not sensitive to hexachlorophane, and the use of hexachlorophane soap cannot be expected to reduce their numbers on the skin.

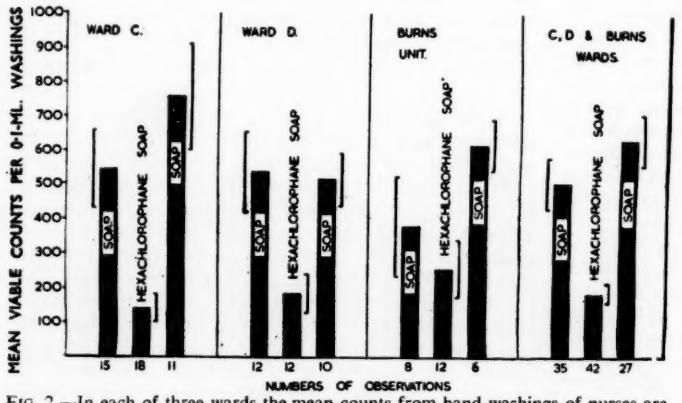


FIG. 2.—In each of three wards the mean counts from hand washings of nurses are shown before, during, and after a period when hexachlorophane soap was used for all ablutions.

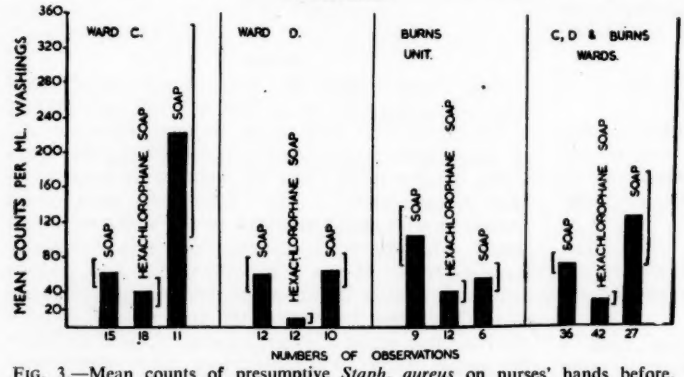


FIG. 3.—Mean counts of presumptive *Staph. aureus* on nurses' hands before, during, and after a period when hexachlorophane soap was used for all ablutions.

Sensitivity to Hexachlorophane of Staphylococci from Nurses' Hands

The minimal inhibitory concentration of hexachlorophane tested by a tube dilution method against 12 strains of *Staph. aureus* varied from 0.07 μg. to 1.5

μg. per ml. These and 12 other strains isolated from nurses' hands before hexachlorophane soap was introduced were tested by a ditch-plate sensitivity test, using 50 μg. of hexachlorophane in the ditch; identical zones of inhibition were shown by all of these strains, and by 33 strains of staphylococci isolated from hands and from the nose during and after the period when hexachlorophane soap was used. By ditch-plate tests there was no hint of the emergence of resistant staphylococci.

Sensitivity tests (to be reported elsewhere) on numerous staphylococci from burns during local prophylactic trials of neomycin, bacitracin, and chlorhexidine showed no evidence of the development of resistance to these agents.

Sensitivity of Nurses' Skin to Hexachlorophane

Apart from a few complaints of dryness of the skin, there was no experience of skin reactions in any of the nurses or laboratory workers who used hexachlorophane soap or phisohex; no reports of sensitivity were received during a period of two months while all the nurses in the burns unit were using hexachlorophane soap.

Discussion

In this paper we describe several alternative methods by which the contamination of operation wounds through holes in gloves might be reduced or even eliminated. Perhaps the combined use of two or more of these methods (assuming they are compatible) might prove more effective than any one of them alone. Like Price (1951), we have found a thorough rinse with 70% ethyl alcohol surprisingly effective, and this effect can apparently be enhanced by including 0.5% chlorhexidine with the alcohol; but the cursory mopping of the skin with a swab soaked in industrial spirit had only a small effect. Regular use of hexachlorophane, especially in the form of phisohex, was very effective and (like the inclusion of neomycin and bacitracin in glove powder) involved no additional manœuvre by the surgeon; indeed, three minutes can safely be taken off the time for scrubbing up when phisohex is used. A further potential advantage in the use of hexachlorophane for all baths and ablutions is the reduction of the general level of the skin flora, so that the risks of contamination of wounds from the skin by other routes—for example, through a wet sleeve of an operating-gown—should also be reduced.

Prolonged scrubbing with soap and water is much less effective than various forms of chemical disinfection, and can damage the skin. It may be argued that the surgeon's scrub is an unnecessary survival and should be abolished. In our studies we have considered the value of antiseptics only in their effect on hands after such a scrub, and it cannot be assumed that the results would have been so good if the hands had not been scrubbed. There is reason to suppose that the physical removal of the loose horny layer may have some value in hand hygiene by making the resident skin flora more accessible to antiseptics.

The use of hexachlorophane soap for nurses' hands was supported by our findings. It involves no additional effort, and has caused no sensitization in the nurses who used it. Phisohex was not included in this part of our study, but from its observed value on the hands of surgeons we may suppose that hexachlorophane in this preparation would be more effective also in suppressing the flora of nurses' hands. The staphylococci—including those which persisted on the skin after the regular use of hexachlorophane soap—were all sensitive to this antiseptic. A worth-while reduction of hand flora could be achieved only by regular and consistent use of the soap; neither hexachlorophane soap used only on duty nor chlorhexidine cream used three or four times a day after washing led to an adequate fall in the numbers of hand staphylococci and other bacteria.

The clinical value of these measures of hand hygiene can only be guessed in the absence of extensive controlled trials with analysis of the incidence of wound sepsis. A number of reports suggest that operation wounds can become clinically infected with staphylococci acquired from the surgeon—for example, McDonald and Timbury (1957), Penikett, Knox, and Liddell (1958), and Mitchell, Timbury, Pettigrew, and Hutchison (1959). Though some of these infections may have been airborne, the risk of infection by contact seems to be of comparable importance, and probably greater when the operation field is small. The importance of the nurse's hand as a vector of infection in the ward is generally recognized. Use of skin antiseptics—for example, hexachlorophane soap—and also, perhaps, of gloves for some ward duties should reduce the amount of clinical infection in the ward; but this, too, can be properly assessed only by controlled trials.

Summary

Viable bacteria emerging through pinholes in surgical rubber gloves and deposited inside the gloves after they had been worn for an hour were counted. These counts were used as criteria in a controlled study of several methods of hand disinfection. By both criteria the mean viable counts from five subjects were approximately halved after five minutes' surgical scrub with soap and water. When the five-minutes scrub was used as a control it was found that viable counts were reduced usually to less than one-tenth by the inclusion of 5 mg. of neomycin and 5 mg. of bacitracin per gramme of glove powder, by a three-minutes rinse with 70% alcohol, by a three-minutes rinse in 70% alcohol containing 0.5% chlorhexidine, and by using hexachlorophane soap or phisohex for the scrub and for all ablutions during the week before the experiment; phisohex was distinctly superior to hexachlorophane soap, and chlorhexidine in alcohol somewhat better than alcohol alone. Mopping the hands with a swab soaked in industrial spirit had a much smaller effect.

The regular use of hexachlorophane soap by nurses in two accident wards and a burns unit was associated with a mean reduction of about two-thirds in the counts of viable bacteria and of presumptive *Staph. aureus* in hand washings. The use of hexachlorophane during periods of duty only, and of chlorhexidine hand cream three or four times a day, was associated with much smaller reduction in the hand flora. The combined use of chlorhexidine cream with hexachlorophane soap for all ablutions did not lead to any consistent improvement upon the results obtained with hexachlorophane soap alone.

All the staphylococci isolated from hands of nurses were highly sensitive to hexachlorophane. No nurses developed sensitivity to hexachlorophane.

We thank the sisters and nurses of the Birmingham Accident Hospital, and members of the laboratory staff, who collaborated in this study. We are also grateful to Mr. W. Cater, A.I.O.T.T., and to the surgeons who supplied us

with gloves for examination, to Messrs. Bayer & Co. for a supply of phisohex, and to I.C.I. (Pharmaceuticals) for a supply of chlorhexidine.

REFERENCES

Barber, M., and Kuper, S. W. A. (1951). *J. Path. Bact.*, **63**, 65.
Cook, J., Parrish, J. A., and Shooter, R. A. (1958). *Brit. med. J.*, **1**, 74.
Devenish, E. A., and Miles, A. A. (1939). *Lancet*, **1**, 1088.
Gillespie, W. A., Simpson, K., and Tozer, R. C. (1958). Ibid., **2**, 1075.
Hufnagel, C. A., Walter, C. W., and Howard, R. W. (1948). *Surgery*, **23**, 753.
Laurell, G. (1959). *Acta paediat. (Uppsala)*, **48**, 125.
Lawrence, C. A., and Erlandson, A. L. (1953). *J. Amer. pharm. Ass., sci. ed.*, **42**, 352.
McDonald, S., and Timbury, M. S. (1957). *Lancet*, **2**, 863.
Mitchell, A. A. B., Timbury, M. C., Pettigrew, J. A., and Hutchison, J. G. P. (1959). Ibid., **2**, 503.
Murray, J., and Calman, R. M. (1955). *Brit. med. J.*, **1**, 81.
Penikett, E. J. K., and Gorrill, R. H. (1958). *Lancet*, **2**, 1042.
—— Knox, R., and Liddell, J. (1958). *Brit. med. J.*, **1**, 812.
Price, P. B. (1938). *J. infect. Dis.*, **63**, 301.
—— (1951). *Ann. Surg.*, **134**, 476.
Seastone, C. V. (1947). *Surg. Gynec. Obstet.*, **84**, 355.
Smylie, H. G., Webster, C. U., and Bruce, M. L. (1959). *Brit. med. J.*, **2**, 606.
Traub, E. F., Newhall, C. A., and Fuller, J. R. (1944). *Surg. Gynec. Obstet.*, **79**, 205.

FALLING ASLEEP OPEN-EYED DURING INTENSE RHYTHMIC STIMULATION

BY

IAN OSWALD, M.A., M.D.

Lecturer, Department of Psychological Medicine, University of Edinburgh; formerly Beit Memorial Research Fellow, Institute of Experimental Psychology, University of Oxford

If one looks at translations of Russian literature in the field of medical psychology one frequently cannot but feel rather lost, for such papers are often couched in terms of the writings of Pavlov.

Pavlov's concepts are not directly compatible with Western neurophysiology, yet, since it is held that those concepts are a guide to therapy and to successful indoctrination, and since, indeed, they have been adopted by Sargant (1951, 1957) to explain sudden political and religious conversion, it is necessary that we should examine Pavlov's writings in order to reconcile them with our own neurophysiological system of knowledge. A partial attempt is made to do so here because the experimental observations with humans to be reported are closely similar to some of the phenomena Pavlov observed in his dogs, and which he believed were manifestations of "internal inhibition" in the cerebral cortex. The "external inhibition" of which he also wrote need not here concern us—it referred to the disorganization of the task in hand by an unexpected and distracting stimulus.

Internal Inhibition

Pavlov was chiefly interested in internal inhibition; "I shall call it simply inhibition, without the adjective, although each time implying internal inhibition" (Pavlov, 1955, p. 232). This inhibition was evoked in the cerebral cortex by any sensory stimulus to which, from the point of view of the dog's general economy or well-being, it was better that the dog should not respond. Throughout Pavlov's writings we find one recurring clue to the nature of this inhibition which it is possible for us to relate to our own system of knowledge—"internal inhibition and sleep are fundamentally one and the same process" (Pavlov, 1928, p. 307). "We observed that as soon as we applied the inhibitory stimulus, a somnolent state of the animal, in the form of drowsiness or sleep, immediately intervened" (Pavlov, 1955, p. 372) . . . "anyone that makes a thorough study of them will be convinced that inhibition and sleep are one and the same phenomenon" (Pavlov, 1955, p. 375).

Transmarginal Inhibition

One means by which the state of inhibition could be produced was by exposing the dog to certain stimuli which would have evoked a response had they not been excessively intense—"such conditioned stimuli too strong to give the maximal conditioned reflex, Pavlov termed transmarginal or supramaximal" (W. H. Gantt, in his introduction to his translation of Pavlov, 1941, p. 14).

Sargant (1951, 1957) interpreted human reactive collapse, after intense mental tension or excitement, in terms of the "transmarginal inhibition" caused by these transmarginal stimuli. This inhibition was held to be protective, and to be manifest in its effect on behaviour by three distinguishable phases, the "equivalent," "paradoxical," and "ultraparadoxical." These appeared when, respectively, all stimuli, whatever their strengths, acted equally; when only the weak stimuli had any apparent action; when the previously elaborated inhibitory agents alone had a *positive* effect. Pavlov wrote of this last, ultraparadoxical, phase as follows: "*In certain stages of drowsiness* [my italics] in normal dogs there occurred a distortion of the effects of conditioned stimuli. The positive stimuli lost their effect, but the negative became positive" (Pavlov, 1928, p. 345). Finally, "after this follows a state of complete inhibition" (Pavlov, 1928, p. 347)—that is, sleep supervened.

It is apparent that not only did Pavlov identify internal inhibition, as most often produced in his laboratory, with sleep, but that the variety he called transmarginal inhibition was believed by him to be of a similar nature

Human Internal Inhibition

In some experiments, described elsewhere (Oswald, 1959), in which electroencephalographic and other physiological variables were recorded, it was found, with larger numbers of human volunteers than it has been possible to use in the experiments to be reported below, (*a*) that signs of sleep appeared in persons subjected to repeated strong electric shocks, (*b*) that signs of sleep could come and go rhythmically in time with regular stimuli at intervals of only a few seconds, (*c*) that signs of sleep appeared while subjects continued to move in time with prolonged, rhythmic music. It is obvious that condition (*a*) could be labelled "transmarginal inhibition," and Sargant (1957) laid great emphasis on the use of prolonged movement, to rhythmic music, as a means of inducing this state of inhibition, quoting with approval the view of Hecker that the state induced is "like that of small animals when they are fascinated by the look of a serpent." This latter condition of fascination, or "animal hypnosis," was shown by Gerebtzoff (1941), and others subsequently, to be electroencephalographically a state of sleep. However, in the experiments with human volunteers mentioned above, the eyes were always closed. Would comparable signs of sleep appear under such circumstances in persons whose eyes were open?

The example borne in mind was that of a prolonged tribal dance where not only does the individual move in time with the rhythm of the auditory stimuli, so

provoking bodily sensations occurring at the same rhythm, but he is stimulated visually, at the same rhythm, by the sight of others moving.

In other experiments, I have encountered some persons who would sleep on undisturbed when their eyes were pulled open during deep sleep beneath a strong light. Again, children may not infrequently be seen asleep with their eyes partly open, particularly during febrile illness. However, it is one thing to be undisturbed by visual stimuli when already asleep, another actually to fall asleep with the eyes open during visual stimulation.

Signs of Sleep

While the most reliable signs of sleep in a normal person are probably electroencephalographic, among other firmly established signs are slowing of the heart (Boas and Goldschmidt, 1932) and pupillo-constriction (Kleitman, 1939; Byrne, 1942).

The electroencephalogram (E.E.G.) of the average alert person whose eyes are open tends to be flat in appearance, with some low-voltage fast waves. If he relaxes with eyes closed, the alpha rhythm, at about 10 c./sec., may appear, but it will do so also if he is bored while his eyes are open, and this is probably related to specific visual inattention. As the individual drowses, the alpha rhythm slows and disappears, the E.E.G. record becomes rather flat again, but with low-voltage slow waves at 4–6 c./sec. As sleep deepens these slow waves are accentuated, and, in many persons, bursts or spindles of faster waves at about 12–15 c./sec. are recorded from the anterior part of the scalp. This last state is one of medium-depth sleep. The stage of a flat E.E.G. record with low-voltage slow waves is generally considered to be sleep, and is the stage, above all others, for hypnagogic hallucinations and dreams; indeed, Dement and Kleitman (1957) maintain that dreams occur only in this stage. The transition from wakefulness to sleep is a gradual and continuous, not an abrupt, discontinuous process.

The Experiments

It was planned that the whole environment of each volunteer should be overwhelmingly (or "trans-marginally") dominated by one major rhythm of stimulation. A 60-minute tape-recording of non-stop "blues" music, with the recording on the upper track of the magnetic tape, was played, and on the lower track of the tape there was recorded by hand a sequence of brief 800 c./sec. tones, which went on and off with each succeeding beat of the musical rhythm. A Brenell Mark V twin-track tape-recorder was used for this. In subsequent experimental sessions both tracks of the magnetic tape were played simultaneously, the upper one into a loudspeaker, and the lower one into a transistorized device containing a high-speed relay which closed during each 800 c./sec. tone (which was inaudible, of course). This relay, in turn, was used to actuate other relays which (*a*) switched on and off the mains supply to the visual stimulator (see below), and (*b*) could deliver repeated electric shocks—in both cases at a rhythm *synchronous* with the rhythm of the music.

The Visual Stimulator.—Visual stimulation was provided by four 60-watt electric-light bulbs, one at each corner of a 2 by 2 ft. (60 by 60 cm.) piece of hardboard, which was otherwise featureless except for a couple of brass screwheads in the centre.

Electric Shocks.—These could be provided from a 0.05-microfarad condenser, rhythmically charged to 300 volts, and rhythmically discharged, through the leg of the volunteer, by means of a double-pole break-before-make relay. A 20-kilohm potentiometer, in series, could be used to adjust the severity of the shock.

The Eyes.—The volunteer subjects' eyes were fixed open throughout the experiments, during which a kettle was kept boiling in the room to minimize corneal drying. Rapid-drying collodion was applied, through a fine nozzle, to a narrow strip of the upper eyelid, about 2 mm. from the margin of the eyelashes. The end of a strip of half-inch (1.25 cm.) adhesive tape was applied to the collodion, and further collodion was placed along the line of contact just clear of the eyelashes. When the collodion had dried, the eyes were opened and the upper eyelid was fixed by attaching the free end of the adhesive tape to the forehead with sufficient tension on each side to prevent the lights of the visual stimulator disappearing from the field of vision, even when the subject voluntarily rolled his eyes upwards to the greatest possible extent.

Volunteer Subjects.—They were paid volunteers who were physically and psychologically normal. They had each, in the past, been subjects in experiments involving electroencephalography, and both their waking and sleeping E.E.G. records were known to be unremarkably normal. Three of the subjects worked in an electroencephalography department and one other was an Oxford undergraduate. Needless to say, they had no history suggestive of narcolepsy.

Experiments with Subjects Immobile

Three volunteers were used in these experiments. The subject lay on a couch with the visual stimulator about 2 ft. (60 cm.) above his face, which meant that there was a peripheral visual field containing, among other detail, equipment, curtains, windows, and myself. Stick-on silver electrodes on the scalp (Fig. 1), and arms, recorded the E.E.G. and E.C.G. Two further electrodes, for electric shocks, were placed on the left leg, one over the lateral surface of the neck of the fibula, in order to stimulate the lateral popliteal nerve fairly directly, and a further one over the anterior surface of the tibia a couple of inches away. The passage of the current between these two electrodes stimulated the lateral popliteal nerve sufficiently to cause a sharp eversion of the foot with each shock, so providing rhythmic proprioceptive as well as rhythmic and sharply uncomfortable skin sensations synchronously with the musical rhythm and the light flashes. The music was always very loud.

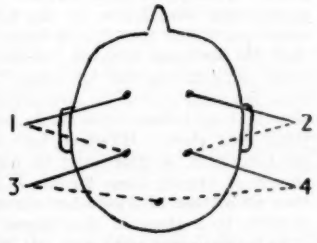


FIG. 1.—Showing positions used for E.E.G. scalp electrodes. The numbers 1–4 in subsequent figures refer to the positions shown here.

Subject A

This subject was a healthy 23-year-old university-educated man who worked in an E.E.G. department. He was very athletic, and his heart rate, when awake at rest, was only 40/min., so that his heart rate of 36–40/min. when asleep did not provide useful information. As this was the first

attempt to observe someone fall asleep with open eyes, this one subject was used when deprived of sleep, after less than one hour's sleep the previous night. The experiment was done at 3 p.m. in a shaded room.

Though accustomed to electroencephalography and rhythmic music, he had never before received electric shocks deliberately, nor the flashing lights. Despite this, his E.E.G. showed him to be lightly asleep after 12 minutes, when there was also some eye-rolling, and he remained asleep (Fig. 2)

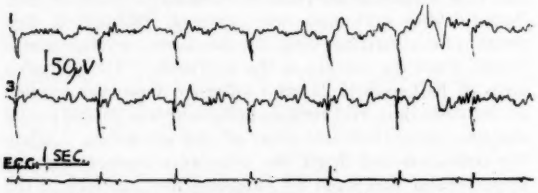


FIG. 2.—Subject A. Eyes glued open during loud music, rhythmic light flashes, and electric shocks. He rapidly went to sleep, characterized by slow waves and 14 c./sec. spindles in his E.E.G., as illustrated. The large spike artifacts in both the E.C.G. and E.C.G. channels occurred as the lights went off; half-way between each of these a small artifact is visible in the E.E.G.—the moment of the shock and the oncoming of the lights.

for the next half-hour, with only intermittent arousal, due to faults in the apparatus which sometimes caused a double electric shock with a consequent break in the rhythm. The session was then ended. His pupil had been noted to be very small while he was asleep, during most of which time he eyes remained motionless in what appeared, from an oblique view, to be the mid-position.

He declared afterwards that he was aware of having been asleep and of once thinking, "The shocks have stopped," and then realizing that, in fact they had not, but that he had been asleep.

Subject B

This subject was not sleep-deprived, and, though the experimental session was held between 9 and 10 p.m., this was several hours before his usual bedtime. He was a 24-year-old Oxford undergraduate, reading psychology and philosophy, a big, hearty, athletic ex-naval officer.

He had been used as a subject in some quite different E.E.G. experiments some months previously, but had never experienced stimulation of the kind used in the present experiments, and complained more about the electric shocks than did the other subjects. As it was evening, the general room illumination was low (one 75-watt bulb 10 ft. (3 m.) from the subject) and the four electric bulbs before his eyes were so bright that at first he declared he could not possibly stand their glare. However, he was assured that he would get used to it in time—and he did. Fig. 3 illustrates the course of events, from the flat E.E.G. record of alertness, through a stage of diminished alertness with return of alpha rhythm, to a stage of drowsiness with low-voltage E.E.G. slow waves (after eight minutes), to unequivocal sleep after another two minutes, though with only a small fall in heart rate, from 72 to 66/min. While he was asleep his pupils were seen to be small, and, seen from an oblique view, appeared central. He was afterwards fully aware that he had been asleep.

Subject C

This subject, a healthy 20-year-old man, worked in an E.E.G. department, and had, some two years previously, received electric shocks in the course of other experiments. He was in no way sleep-deprived, and the experiment was conducted during the afternoon in a shaded room.

The course of events was similar to that with Subject B. He was asleep within eight minutes (Fig. 5), and after a further 15 minutes was aroused by a double shock (caused by an apparatus fault) which destroyed the rhythm. After this he remained drowsy for another 15 minutes till the session ended. During much of the latter period his basic E.E.G. record, as it were, was that of light sleep—that is,

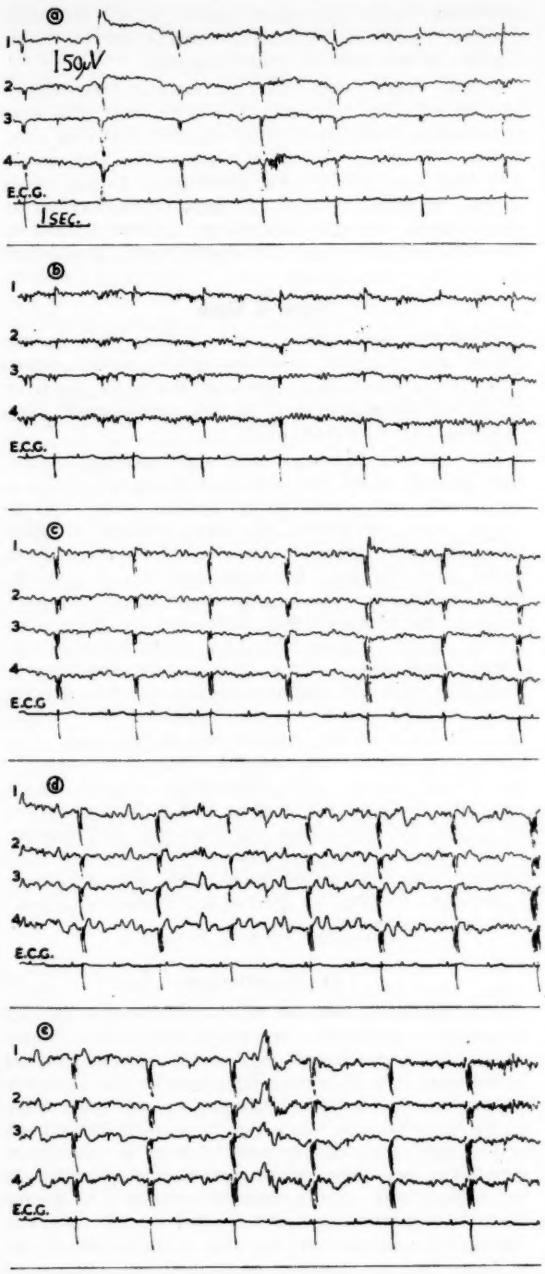


FIG. 3.—Subject B. Eyes glued open. Rhythmic electric shocks and lights. Large artifacts at time of lights off, small artifacts at time of lights on and shock.

(*a*) Top excerpt shows E.E.G. appearance after 1 minute. Note flat record with low-voltage fast waves—the normal appearance in a waking person with eyes open.

(*b*) Second excerpt, after 4½ minutes. Over the back of the head (channel 4 especially) alpha rhythm has reappeared even though the subject's eyes are open.

(*c*) Third excerpt, after 8 minutes. The E.E.G. appearances are now those of very light sleep. The alpha rhythm has disappeared and low-voltage slow waves can be seen.

(*d, e*) After 8 minutes the subject is asleep (bottom two excerpts) and the E.E.G. record is dominated by slow waves and occasional K-complexes appear (the big slow wave followed by 12-c./sec. waves) and anterior 15-c./sec. sleep spindles (channels 1 and 2). His pupil was by now very small.

flat with low-voltage slow waves—but each light flash tended to cause him to alternate between three-quarters of a second in light sleep and three-quarters of a second in a more aroused state in which alpha rhythm was present (Fig. 6).

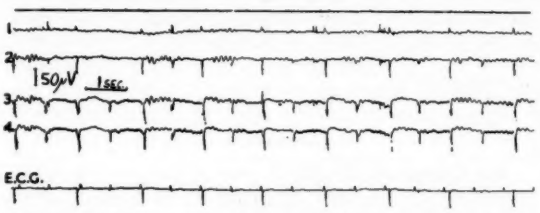


FIG. 4.—Subject C. Eyes glued open, rhythmic music, electric shocks, and light flashes. After three minutes the E.E.G. record is no longer that of continuous full alertness. The alpha rhythm may be seen, in channels 3 and 4, to appear at times when the lights are off. The big artifacts indicate lights off, the smaller ones indicate lights on. While the lights are on, some 50-c./sec. mains interference occurs.

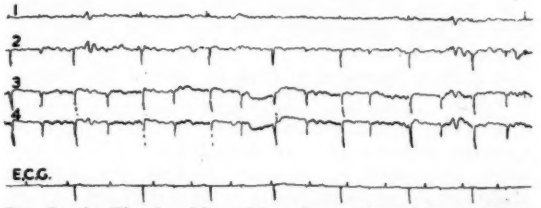


FIG. 5.—As Fig. 4. After eight minutes the subject is lightly asleep and his E.E.G. record is one of low-voltage slow waves. Occasional 12-c./sec. sleep spindles (not shown) also occurred.

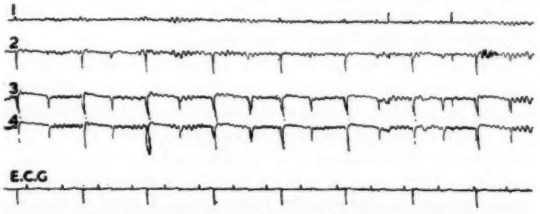


FIG. 6.—As Figs 4 and 5. The subject was aroused by an unintended double shock, and has drowsed since; in contrast to Fig. 4, his alpha rhythm now tends to return when the light is on (during the thick, heavy 50-c./sec. artifact), which rhythmically brings him from, as it were, a state of light sleep to one of low-grade wakefulness

This was in contrast to the first few minutes of the session, when the light had tended to make him alternate between a very alert (light on, no alpha rhythm) state and a less alert (alpha rhythm present) state (Fig. 4).

While his E.E.G. showed signs of sleep, his pupils were seen to be small and rolled upwards, though not sufficiently to obscure the pupils. His heart rate, which had been 80–85/min., fell to 55–65/min.

He subsequently reported that he was quite aware of having been asleep for part of the session.

Experiments with Subjects Actively Moving

The experiments already described involved rhythmic leg movement to the music, but this was really passive movement caused by the electric stimulation. Two further sessions were undertaken in which subjects did not receive electric shocks but actively banged both arms up and down from the elbows, while sitting up in a chair, and tapped both feet in time with the rhythm of the music and the flashing lights.

The visual stimulator was again positioned about 2 ft. (60 cm.) in front of the eyes, which, as before, were glued and strapped fully open. Both sessions took place during the afternoon, neither subject was sleep-deprived, and the room was shaded but not darkened.

Subject C

In the first few minutes his E.E.G. was the fairly flat record characteristic of full alertness with the eyes open, though within seven minutes his alpha rhythm had become fairly continuous and a little slow activity was beginning momentarily to appear. After 10 minutes there came the first break in movement lasting three seconds, and this was associated with the E.E.G. slow-wave picture of light sleep. In the next 15 minutes there were 65 episodes, lasting 3–20 seconds, of failure to move in time to the music, each one associated with E.E.G. signs of light sleep and a considerable slowing of the heart (see Fig. 7). In these episodes of light sleep his eyes were rolled upwards, but not enough to obscure the pupils.

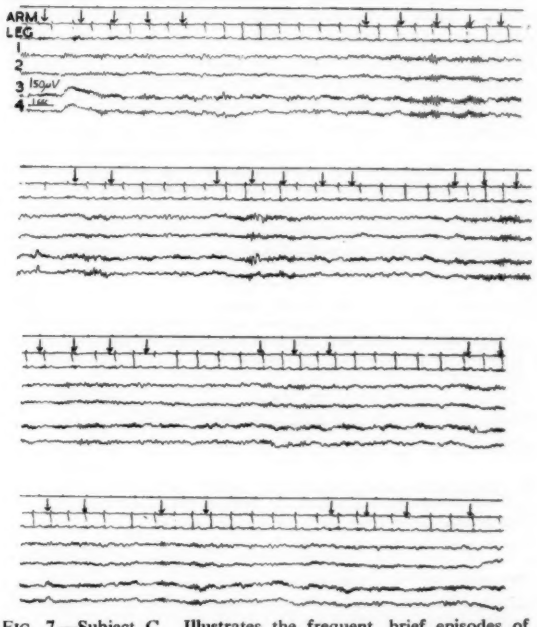


FIG. 7.—Subject C. Illustrates the frequent, brief episodes of light sleep, during which the E.E.G. alpha rhythm disappears, to give place to low-voltage slow waves, the heart slows (the E.E.G. is present in the arms and leg channels) and movement ceases. The arrows point to bursts of muscle potentials with each movement. The heavy 50-c./sec. interference in channel 3 indicates when the lights were on. The segments of record are continuous from above down. Electrodes over the forearm muscles and over the gastrocnemius and peronei show bursts of muscle spikes from the leg and arm in this and subsequent figures.

Questioned afterwards, he said that once or twice he had "come to" suddenly and realized that he might have been asleep. He had had to urge himself to keep moving. Asked if he thought he had stopped much, he said, "Yes, but not more than half a dozen times."

Subject D

This subject, a 24-year-old healthy university-educated man, worked in an E.E.G. department. He moved uninterruptedly to the music for 15 minutes, during which time his alpha rhythm gradually became more or less continuously present, after which the first break in arm movement occurred, associated with a few seconds of E.E.G. signs of light sleep. Further breaks in movement, 52 in all, each associated with E.E.G. signs of sleep and usually an obvious slowing of the heart, occurred in the next 25 minutes. Fig. 8 illustrates. The episodes of sleep were associated with small pupils and a variable position of the eyes, which would roll to one side for perhaps 10 seconds, then perhaps upwards (but still with exposed pupil) for a like period, then else-

where, and so on. The breaks in movement bore no obvious relation to the position of the eyes.

Questioned afterwards, he emphatically maintained that he had stopped moving only once. He said that, at first, luminous geometrical patterns had seemed to be present on the hardboard of the visual stimulator, but later he became unaware of seeing anything.

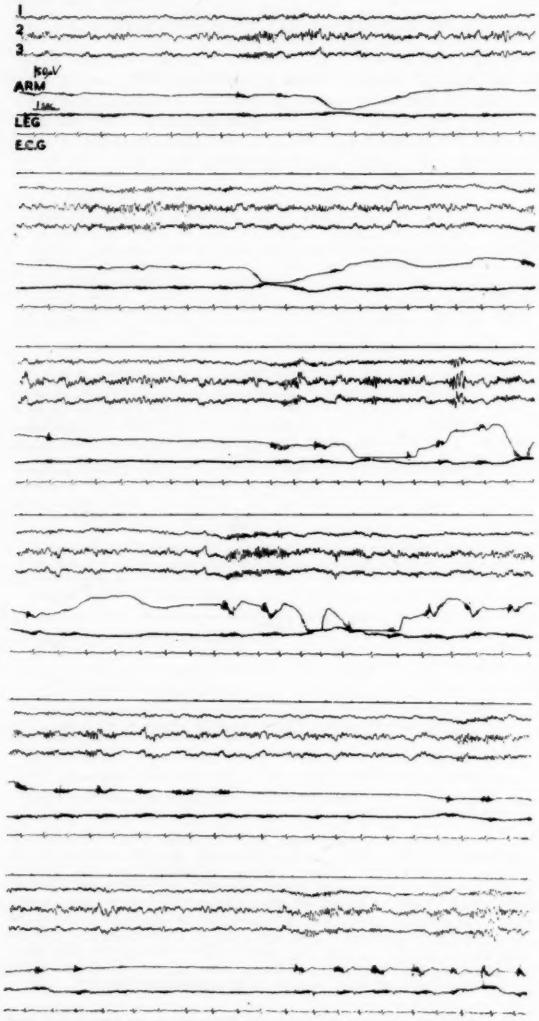


FIG. 8.—Subject D. Eyes glued open while moving actively to rhythmic music and rhythmic light flashes. Illustrating how repeated brief episodes of light sleep were manifested by slow waves in the E.E.G., some slowing of the heart, and failure of movement. Bursts of muscle spikes can be seen to persist longer in the leg than in the arm channel. Just before each return of movement, after a sleep episode, the sleep pattern changes momentarily to a low-voltage fast pattern prior to the alpha rhythm return. The segments of record are continuous. Channel 2 of the E.E.G., in this instance, derived from the front right and the nearmost electrode.

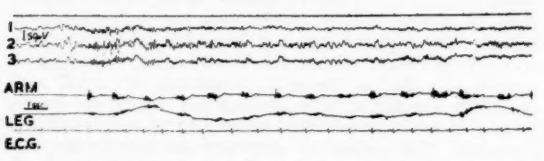


FIG. 9.—As Fig. 8, but to illustrate how, at times, movement continued when the E.E.G. record was, nevertheless, dominated by slow waves.

Compared with experiments previously conducted on volunteers with closed eyes (Oswald, 1959), Subjects C and D tended much more often to cease moving altogether during E.E.G. sleep signs, whereas subjects with eyes closed more often went on moving during similar E.E.G. signs, even though the quality of movement deteriorated. Nevertheless, as may be seen in Fig. 9, there were times when movement continued while the subject's E.E.G. contained a good deal of slow activity.

Discussion

The changes in the E.E.G. seen in the present experiments, which are those characteristic of persons falling asleep under conventional circumstances, were accompanied by slowing of the heart in three of the four subjects, and by obvious pupillo-constriction in also three of four subjects. Furthermore, the subjects in the experiments involving shocks were all quite certain they had been asleep. This was in contrast to the two subjects who moved to the music. The obvious difference between these circumstances was that in the former case subjects slept for minutes at a stretch, while in the latter case subjects appeared to sleep for only a few seconds at a time.

It seems reasonable to believe that each of these volunteer subjects did go to sleep, but it will be remembered, that there is no clear dividing line between wakefulness and sleep, and it is no part of my present concern to insist that subjects crossed any such dividing line, only to claim that there was a considerable fall of cerebral vigilance, and a large decline in the presumptive ascending facilitation from the brain-stem reticular formation to the cerebral cortex.

The eyes of two of the four subjects remained fairly central, and only in one case were the eyes steadily turned upwards. Upward rotation is common, though far from universal, during sleep (Pietrusky, 1922), but Kleitman (1939) noted that if the eyelids were opened and then kept apart during sleep the eyes would sometimes return to the middle position, as I have also seen in other experiments.

The problem which led to the present experiments has already been mentioned—namely, whether intense rhythmic stimulation would produce a sleep-like condition in persons whose eyes were open, for this condition could then be related to the transmarginal inhibition of Pavlov, which Sargant believed developed as a result of intense rhythmic stimulation. The importance of this lies in the differences in the *quality* of thinking between the fully awake state and drowsiness or light sleep. We believe to-day that, other things being equal, fully efficient cortical activity depends upon an optimal, high degree of ascending facilitation from the brain-stem reticular formation. Lesser degrees of that facilitation would be associated with impaired capacity for higher-quality thinking. One of the characteristics of the latter is that numbers of more or less independent facts can be simultaneously related together—in particular, facts derived from the past can be related to current or projected activities or beliefs.

McKellar (1957) has drawn attention to the differences between thinking in the fully alert condition and thinking in light sleep—that is, dreaming—the former "reality-adjusted" thinking, and the latter illogical, "autistic" thinking, which is no longer governed by "repeated appeal and submission to established fact, whether perceived or stored" (Oldfield, 1959).

Autistic thinking in dreams, though illogical, perhaps confused, yet intensely personal, does not quite conform to the "ultraparadoxical" behaviour during drowsiness that Pavlov described, and on which Sargant drew to exemplify, for instance the new love for a formerly hated interrogator, during the state of transmarginal inhibition. Scrutiny of Pavlov's writings, however, leaves some doubt on how firmly established and clearly demarcated were the three phases he distinguished, and even more doubt on how confidently these changes in the salivary secretion of dogs, in the particular circumstances of Pavlov's laboratory, should be extrapolated to human behaviour. It would seem safer merely to recognize that in certain phases of drowsiness the dogs failed to respond in their usual way to stimuli of learned significance, and that the dogs' behaviour became illogical, disorganized, and confused.

The present experiments have illustrated the effects of extremely monotonous sensory stimulation on persons required to *keep still* or make only repetitive movements —the former factor is very important, as discussed elsewhere (Oswald, 1959). Yet there can be little doubt that changes of the same kind, if of lesser degree, must inevitably occur in persons engaged on other monotonous tasks. Apparently trade union opinion was against an unaccompanied driver for diesel locomotives, and one may be glad that the man who has to sit at the front of the train, subjected to its rhythmic chatter, the sight of telegraph poles flashing by, and the rails and sleepers disappearing endlessly below has someone else with him to provide occasional conversation—in fact, to introduce some variety, and help to prevent a state developing similar to that seen in Subjects C and D, who, though aware only occasionally of "coming to," yet went to sleep so frequently.

What physiological mechanisms underly this response to monotony? Let it be accepted that the degree of wakefulness/sleepiness depends on the level of excitement of the activating system in the brain-stem reticular formation, and the amount of consequent ascending facilitation from it to the cortex. Let it be accepted also that that activating system is kept excited by impulses arriving either directly or indirectly as a result of stimulation of sense organs. If the impulses were to become repetitively monotonous, what would be expected to happen? There is every reason to suppose that the usual response—namely, excitement of the activating system—would no longer appear, for this phenomenon of *habituation*, or cessation of response on repeated stimulation, is a property of stimulus-response mechanisms of all degrees of complexity (Humphrey, 1933; Oldfield, 1937). Characteristic of this failure of response is the immediate restoration of response, or *dishabituation*, following a change such as an alteration in the rhythm of stimulation—and in the present experiments the arousal reappeared on several occasions when an unintended double electric shock was given.

Hugelin and Bonvallet (1957) have presented evidence to indicate that cortico-fugal impulses can damp down the activating system in the brain-stem reticular formation. In the case of a person who is obliged to keep still and who knows he can do nothing about the sensory stimulation, perhaps inhibitory, "Keep still! Don't move!" signals from cortex to brain-stem might well play a part in causing sleep, as is presumably the case in the rabbit fascinated by the snake.

Summary

Pavlov wrote of the basic identity of sleep and states of inhibition caused by certain forms of sensory stimulation.

Experiments are described in which male volunteers, whose eyes were glued widely open, went rapidly to sleep during simultaneous, *synchronized*, rhythmic electric shocks, loud rhythmic music, and strong flashing lights. Active rhythmic movement to the music, in place of the shocks, also appeared to cause subjects to sleep very briefly for a few seconds at a time, often with moments of failure to move in response to the rhythmic music—moments of which the subjects were subsequently largely unaware.

The significance of these observations is discussed in the light of Sargant's proposals concerning "transmarginal inhibition" in humans, and attention is drawn to the failure of "reality-adjusted" thinking in states of light sleep, and also to the almost inevitable occurrence of similar brief episodes of light sleep in persons, such as some drivers, who are exposed to prolonged, monotonous sensory stimulation.

I wish to acknowledge the encouragement and facilities given me by Professor R. C. Oldfield, and to pay tribute to the fortitude of the volunteer subjects. Mr. P. G. M. Dawe kindly made the transistorized high-speed relay device.

REFERENCES

Boas, E. P., and Goldschmidt, E. F. (1932). *The Heart Rate*. Thomas, Springfield, Ill.
Byrne, J. G. (1942). *Studies on the Physiology of the Eye*. Lewis, London.
Dement, W., and Kleitman, N. (1957). *Electroenceph. clin. Neurophysiol.*, **9**, 673.
Gerebtzoff, M. A. (1941). *Arch. int. Physiol.*, **51**, 365.
Hugelin, A., and Bonvallet, M. (1957). *J. Physiol. (Paris)*, **49**, 1171.
Humphrey, G. (1933). *The Nature of Learning*. Kegan Paul, London.
Kleitman, N. (1939). *Sleep and Wakefulness*. University of Chicago Press, Chicago.
McKellar, P. (1957). *Imagination and Thinking*. Cohen and West, London.
Oldfield, R. C. (1937). *Brit. J. Psychol.*, **28**, 28.
—— (1959). Ibid., **50**, 74.
Oswald, I. (1959). *J. ment. Sci.*, **105**, 269.
Pavlov, I. P. (1928). *Lectures on Conditioned Reflexes*. Translated by W. H. Gantt. Liveright Publishing Corporation, New York.
—— (1941). *Lectures on Conditioned Reflexes*. Volume 2. *Conditioned Reflexes and Psychiatry*. Translated by W. H. Gantt. Lawrence and Wishart, London.
—— (1955). *Selected Works*. Foreign Languages Publishing House, Moscow.
Pietrusky, F. (1922). *Klin. Mbl. Augenheilk.*, **68**, 355.
Sargant, W. (1951). *Brit. med. J.*, **2**, 311.
—— (1957). *Battle for the Mind*. Heinemann, London.

In its Tenth Report the W.H.O. Expert Committee on Addiction-producing Drugs recommends that eight new substances derived from different chemical groups and all having morphine-like effects should be subject to international control—allylprodine, benzethidine, furethidine, levophenacylmorphan, metazocine, norlevorphanol, phenazocine, and piminodine. The committee feels that the fundamental criterion for the establishment and degree of control is the extent to which drug-induced behavioural disturbances are a risk to the community, for neither the chemical structure *per se* nor any definition, however descriptive, can be a complete guide to which substances should be placed under control. It strongly urges that research on drug addiction should be strengthened and expanded, since it continues to be a serious international public-health problem. (*World Health Organization: Technical Report Series*, 1960, No. 188. Available from H.M.S.O., P.O. Box 569, London, S.E.1, price 1s. 9d.)

SMOKING AND PERSONALITY*

BY

H. J. EYSENCK, Ph.D.

Institute of Psychiatry, London

MOLLIE TARRANT, B.A.

MYRA WOOLF, B.Sc.(Econ.)

AND

L. ENGLAND

Mass Observation

The discovery of a *statistical* association or correlation between lung cancer and smoking (Doll and Hill, 1952, 1954; Hammond and Horne, 1954; Stocks and Campbell, 1955; Berkson, 1958) has led some investigators to put forward the hypothesis that a causal relationship exists between these two factors. This hypothesis has been severely criticized by Fisher (1959), Berkson (1958), and others, on the grounds that alternative and equally plausible theories existed and had not been disproved. These critics further pointed to various weak points in the causal argument, such as the fact that inhaling does not aggravate the alleged effects of smoking, but, on the contrary, appears to have, if anything, an ameliorating effect; that pipe smoking does not appear to have the same effects as cigarette smoking; or that smoking has a statistical association not only with cancer but also with other diseases which had never been conceived to have the same aetiology as cancer.

The main hypothesis which has been put forward to account for the correlation, other than that of direct causation, has been Fisher's suggestion "that a common cause supplies the explanation"—that is, that both rate of smoking and proneness to lung cancer are due to some third variable underlying both; "the obvious common cause to think of is the genotype." He goes on to say that "if there is any genotypic difference between the different smoking classes we may expect differences in the type or frequency of the cancers that they display." Why, he asks, do some people take to the pipe rather than to cigarettes, while others make the opposite choice? "Because they are made that way." In other words, innate personality features determine our behaviour with respect to smoking, at least in part, and they also determine our proneness to lung cancer. In spite of the fact that there is no real evidence in favour of this hypothesis, it cannot be dismissed out of hand; it suggests new experiments to throw more light on possible genotypic differences between different groups of smokers. It was with the intention of supporting or confirming certain hypotheses related to this general theory that the present research was undertaken.

Theoretical Analysis

A survey of the literature disclosed little that was of help in planning the investigation (McArthur, Waldron, and Dickinson, 1958), and accordingly recourse was had to theoretical considerations related to the general dimensional theory of personality (Eysenck, 1947, 1952, 1957, 1960a, 1960b). Three main hypotheses were advanced, as well as two minor ones. The terms used in stating these hypotheses ("extraversion," "neuroticism," "rigidity") have been defined in terms of this theory and are not here redefined; the reader is referred to the references just cited for a detailed account.

According to the first hypothesis, smoking habits should be related to extraversion in the sense that the number of cigarettes smoked would increase with degree of extraversion. This hypothesis was derived from the well-known characteristic of the extraverted personality to concentrate on objects in the *outer world*, in contrast to the introvert, who tends to be preoccupied with his own thought processes and other *internal states*. According to this hypothesis one would expect extraverts to be particularly heavy consumers not only of cigarettes but also of alcohol, sweets, and other pleasure-giving objects in the external world.

The second hypothesis was to the effect that the more emotionally unstable, neurotic type of person would be the heavier smoker because smoking, like many other motor and sensory habits, reduces the strength of an aroused emotion. Consequently, for a person of this type cigarettes would become a solace and might almost be regarded in the light of a medicine.

The third general hypothesis investigated related to the personality trait of rigidity, where it was postulated that the more rigid person would be less likely to smoke. This was deduced from the fact that smoking, as indeed all pleasurable activities, tends to be regarded as slightly sinful, and would therefore tend to be shunned by the rigid, puritanically minded type of person.

The Experiment

The Questionary

To test these hypotheses, a questionary was constructed which contained questions which in previous work had been found to be good, reliable, and reasonably valid measures of these personality traits (Eysenck, 1959; Nigniewitzky, 1955); this questionary is printed in the Appendix (p. 1460).

In addition to these general hypotheses, two items were included to test quite specific hypotheses; to wit, items 7g and 8g—that is, 7g: Do you get so excited that you use your hands when you talk? and 8g: Do you have any habits like chewing pencils or biting fingernails or things like that? As regards 7g, use of hands when talking, the hypothesis was that the natural impulse of people to use their hands would be somewhat inhibited by having a cigarette as an alternative outlet, so that non-smokers would use their hands more. Similarly, it was assumed that non-smokers would be more likely to chew pencils and bite their fingernails than smokers, who, after all, have an alternative outlet.

Sample Tested

The design of the experiment makes use of 24 groups of subjects divided equally on the basis of age (40–59 and 60–70), class (ABC and DE), and smoking habits (non-smokers, light, medium, and heavy smokers, pipe smokers, and ex-smokers). The hypotheses only deal with the relative positions of *four* groups—namely, the non-smokers and the light, medium, and heavy smokers; no prediction could be made with respect to ex-smokers

*In the summer of 1958 Mass-Observation Ltd. was commissioned by the Tobacco Manufacturers' Standing Committee to carry out a survey to test certain hypotheses on the personality characteristics of smokers and non-smokers suggested by Professor H. J. Eysenck. The main results of the study (Mass-Observation, 1959) are summarized in this paper.

or pipe smokers. There are 100 subjects in each of the groups except among the older non-smokers; for purposes of analysis, scores in these groups have been pro-rated so as to be comparable in all respects with the other groups.

The object of the sample design was to obtain an analytic (as opposed to a representative) sample of men. For the purposes of analysis, it was decided to interview 400 men in each of six smoking groups (light, medium, and heavy cigarette smoker, pipe smoker, non-smoker, and ex-smoker) so that, within each smoking group, there were 100 men in each of two classes and two age-groups. In detail the requirements were as shown in Table I.

TABLE I

	Class ABC		Class DE	
	40–59	60–70	40–59	60–70
Light ..	100	100	100	100
Medium ..	100	100	100	100
Heavy ..	100	100	100	100
Pipe	100	100	100	100
Ex-	100	100	100	100
Non- ..	100	100	100	100

For each subgroup the selection of informants was to be randomized as much as possible, though the sampling method used was quota sampling.

In the final event, it proved impossible within the time and cost limits of the inquiry to contact 100 non-smokers in the older age-groups, and the numbers analysed were 70 in Class ABC and 90 in Class DE. To obtain the numbers required for the experimental sample, the approximate number of contacts finally made was over 7,000.

A three-stage sampling design was employed. At the first two stages the method of selection of units was random. The general plan was as shown in Table II.

TABLE II

Stage	Stratification Factors	Notes
1. Administrative districts	(*a*) Geographical region (6) (*b*) Conurbation/urban/rural (*c*) J-index	Selection of individual areas within each stratum was made with a probability proportionate to its size
2. Wards ..	J-index	
3. Individuals ..	Quota controls: (*a*) Age (*b*) Class (*c*) Occupation	

Stage 1.—100 administrative districts were selected as first-stage units. Before selection, the districts were stratified into six geographical regions and three urban/rural breakdowns. Within each stratum, the administrative districts were listed in order of their J-index, and the list was divided into two groups of approximately equal size. An equal number of administrative districts were selected from each part of the list, and the selection of individual administrative districts was made with a probability proportionate to its size. As no J-index exists for areas in Scotland, the selection of administrative districts within each geographical/urban, etc., stratum was made randomly.

Stage 2.—The second stage of sampling was to select three wards from each of the larger (population 50,000+) administrative districts selected at the first stage. In the smaller administrative districts a 100% sample—that is, *all* the wards within each administrative district—were selected for investigation. Selection of individual wards was made in a way similar to the selection of administrative districts. The wards within each district were listed in order of their J-index, and the list was divided into three groups of approximately equal size. One ward was selected from each group. It is not always usual, when using the method of quota sampling, to use a second sampling stage. Generally, interviewers are instructed to spread their interviews over the whole of the first-stage unit, whatever it might be. For this survey, however, it was thought preferable to provide some method of making certain that the interviews were not clustered in one part of the larger administrative districts, and this was done by selecting second-stage units which ensured that the interviews were carried out in three different parts of the towns concerned.

Stage 3.—At the final stage the selection of individuals to be interviewed was not made randomly, but by the method of quota sampling. Interviewers were allocated quotas on age, social class, and smoking group, so that information was obtained from the required respondents. A looser control was placed on occupation so that the distributive trades were not overrepresented, as tends to be the case with quota sampling.

Allocation of Subjects

Subjects were allocated to one of six groups on the following basis.

Light smokers were taken to be those who said that they smoked 14 or fewer cigarettes daily.

Medium smokers were taken to be those who said that they smoked between 15 and 24 cigarettes daily.

Heavy smokers were taken to be those who said that they smoked 25 or more cigarettes daily.

Pipe smokers were taken to be those who smoked a pipe only, or, if they had more than one smoking outlet, accounted for more than three-quarters of their total consumption in pipe tobacco.

Ex-smokers were taken to be those who did not smoke at present but who claimed that, in the past, they had smoked at a rate equivalent to more than one cigarette a day or 2 oz. (57 g.) of tobacco in two months for at least as long as a year.

Non-smokers were those who did not smoke at present and claimed that in the past they had not smoked more than one cigarette a day or more than 2 oz. (57 g.) of tobacco for at least as long as a year.

Throughout, a conversion factor of 1 oz. (28.3 g.) of tobacco as the equivalent of 30 cigarettes was used. This factor was used to categorize those who hand-rolled their cigarettes, into light, medium, and heavy cigarette smokers, and also to assess the relative strength of pipe and cigarette smoking among those who smoked both. Those whose consumption of tobacco was at least three-quarters in pipe tobacco were classified as "pipe" smokers; those whose consumption was at least three-quarters in cigarettes were classified as cigarette smokers in the relevant category of light, medium, or heavy, depending on the number of cigarettes smoked. Those in between these two groups—that is, those who smoked about an equal amount in both pipes and cigarettes—were *omitted from the sample.*

Unreliability of self-assessments may serve to reduce the final relationships discovered, but it has been shown that the reliability of such statements about smoking habits as were called for by the present research design

is reasonably high (Todd and Laws, 1958); it is doubtful if the fact that self-assessments were asked for constitutes a major weakness of this study.

Results

Individual Questions

The first analysis to be carried out was done on each question separately. Scores were derived by giving two points to each "Yes" answer and one point to each "?"; no points were given to "No" answers. An analysis of variance was then carried out for each of the questions, both for main effects and for interactions. In this way it was possible to discover for each question whether the answers showed significant differences associated with class, age, or smoking habits (main effects); and it was also possible to determine whether there was any interaction between some of these main effects, such for instance as is described later in connexion with question 7g, where it was found that the tendency to use one's hands while talking was indeed associated significantly with non-smoking, but only in the lower social groups. The analysis revealed that age was much the most important variable in determining response differences, and that class was relatively unimportant. Smoking habits uncomplicated by interaction effects appeared significant in connexion with five questions (6f, 8d, 8f, 8g, 8h) and twice in connexion with interaction effects involving age (8b, 7g). It is clear from these analyses that individual questions on their own do not differentiate the groups very efficiently so far as smoking habits are concerned. This is not unexpected, because single questions are relatively unreliable; it is only when they are combined in groups that these unreliabilities are reduced owing to the cancelling out of chance errors.

Details of results are given in Table III. Three of the questions relate to extraversion, and in each case non-smokers, as predicted, are more introverted than cigarette smokers. Pipe smokers are relatively introverted, while ex-smokers are similar to medium smokers. On the one question relating to rigidity, non-smokers are the most rigid group, as predicted. On the one question relating to neuroticism, ex-smokers emerge as the most neurotic; smokers as a whole do not appear to be more neurotic than non-smokers.

As regards the two questions concerning which special hypotheses were advanced, the results are as follows. On question 7g the hypothesis that non-smokers would use their hands more when talking than would smokers is verified only in the working-class group and not in the middle-class group; the class-group interaction is significant. On question 8g the hypothesis that non-smokers would have more chewing and biting habits than smokers is verified; only ex-smokers excel non-smokers in this.

Determination of Trait Scores

The next step in our inquiry was the carrying out of a factor analysis of the correlations between the different personality questions. This was done in order to obtain direct evidence from the data of this inquiry of the feasibility of combining questions into groups. This was a necessary process, since combinations should not be arbitrary, or determined by previous analyses on different groups, and it seemed desirable to check on their applicability to this particular sample.

To ascertain the precise grouping of the inventory items, correlations were calculated between all 31 items, age, class, and smoking. These correlations were then factor-analysed in order to determine the grouping, and four factors were extracted by means of Hotelling's principal components method. This solution was then rotated according to Thurstone's simple structure solution, and revealed three clear-cut factors. The first of these was *extraversion*, defined by items 5d, 6f, 6g, 7f, 8b, and 8h. The second factor was one of *rigidity*, defined by items 6b, 7a, 7b, 7e, 8e, 8f, and 8i. The third factor was one of *neuroticism*, made up of items 5b, 5c, 5e, 5f, 6a, 6d, 6e, 6h, 7c, 7d, 8a, and 8d.

Scores were next calculated for each of these three factors according to the following scheme. For the extraversion and rigidity factors, the answer "Yes" on each of the items defining the factor is scored two points, the answer "No" is scored zero points, and any other answer is scored one point. The same scheme is followed in calculating the neuroticism score, except that for item 6a the answer "No" is scored two points, the answer "Yes" no points, and any other answer one point. These three scores are independent of each other; when they were correlated over the whole population, neuroticism and extraversion correlated 0.04, neuroticism and rigidity correlated 0.09, and extraversion and rigidity correlated 0.07.

Personality Traits and Smoking Habits

Mean scores were next calculated on the three factors separately for the various groups of smokers, subdivided by age and sex. Detailed figures may be consulted in the

TABLE III

Question	Trait	Non	L	M	H	P	Ex	F_C	F_A	F_G	F_{AG}	F_{CG}
6f. Would you rate yourself a lively individual?	E	529	553	612	624	544	556	0·053	0·854	**4·819**		
8d. Are you frequently lost in thought, even when you're supposed to be taking part in a conversation?	N	287	308	290	263	301	340	0·756	1·323	*3·100*		
8f. Do you always prefer the familiar, the safe and sure, to taking chances with the new and untried?	R	541	505	492	445	485	455	**37·297**	**79·135**	**5·652**		
8g. Do you have any habits like chewing pencils or biting finger-nails or things like that?	S.H.	116	80	106	76	62	122	0·354	**19·060**	*3·879*		
8h. Are you inclined to be quick and sure in your actions? ..	E	586	582	588	640	544	588	**12·301**	**24·214**	*3·847*		
8b. Are you happiest in some scheme that calls for rapid action? ..	E	445	459	488	520	438	478	5·732	**147·140**	*8·879*	*5·234*	
7g. Do you get so excited that you use your hands when you talk? ..	S.H.	196	183	149	197	167	163	2·496	**137·571**	*5·140*		*6·500*

E = Extraversion. N = Neuroticism. R = Rigidity. S.H. = Special hypothesis. Non = Non-smoker. L = Light smoker. M = Medium smoker. H = Heavy smoker. P = Pipe smoker. Ex = Ex-smoker. F = F ratio. C = Class. A = Age. G = Smoking groups. Figures in italic: significant, 5%. Figures in bold type: significant, 1%.

original report (Mass Observation, 1959); for reasons of space, only the results of the analysis of variance are here given.

Extraversion.—The mean scores for non-smokers and light, medium, and heavy smokers are 7.016, 7.133, 7.445, and 7.805, giving a grand mean for these four groups of 7.358. The means increase with an increase in smoking as required by the hypothesis. The mean for the pipe smokers is 6.96, that for ex-smokers 7.27. (No predictions were made for these groups, and consequently they will not be included in the analysis of variance to determine the significance of the relationship between smoking and personality.) An analysis of variance was carried out to determine the significance of the relationship found between extraversion and smoking; the results are given in Table IV. As the

TABLE IV.—*Analysis of Variance Table. Extraversion and Smoking*

	Degrees of Freedom	Sum of Squares	Mean Squares	Variance Ratio
Between groups ..	3	145·3082	48·4361	4·728
Within ,, ..	1,556	15,938·9510	10·2435	
Total ..	1,559			

P=0·01.

results are significant beyond the 1% level, the hypothesis may be regarded as established. We can now carry out individual t tests to establish significance of differences between groups. The difference between non-smokers and medium smokers is significant at the 5% level on a one-tail test; that between non-smokers and heavy smokers is significant at the 5% level; other differences are not significant.

Rigidity.—The mean scores for non-smokers, light, medium, and heavy smokers are 9.456, 9.285, 9.233, and 8.930, with a grand mean for these four scores of 9.220. It will be seen that the scores decline with an increase in smoking as required by the hypothesis. (The mean for pipe smokers is 9.01, that for ex-smokers is 9.23. Again, these groups will be disregarded in calculating the significance of results, as no predictions were made regarding them.) An analysis of variance was carried out, and is reported in Table V. It will be seen that the result is just

TABLE V.—*Analysis of Variance Table. Rigidity and Smoking*

	Degrees of Freedom	Sum of Squares	Mean Squares	Variance Ratio
Between groups ..	3	55·5572	18·5191	2·594
Within ,, ..	1,556	11,107·9878	7·1388	
Total ..	1,559			

P=0·05 .. { Actually 2·60 required

about significant at the 5% level, and we may therefore calculate t tests to establish significance between single groups. The differences between light and heavy smokers and between non-smokers and heavy smokers are significant at the 5% and 1% levels respectively on a one-tail test; none of the other differences are significant. We may consider our hypothesis supported, but not as strongly as in the case of extraversion.

Neuroticism.—The mean scores for non-smokers, light, medium, and heavy smokers are 8.274, 8.270, 8.445, and 8.455, with a grand mean of 8.368. (Pipe smokers have a mean of 8.22 and ex-smokers one of 8.43. These two scores not having been predicted are not included in the analysis of variance.) An analysis of variance was performed, and is given in Table VI. It will be seen that while the score on neuroticism increased as predicted with the amount of smoking, the results are not significant. It is possible that

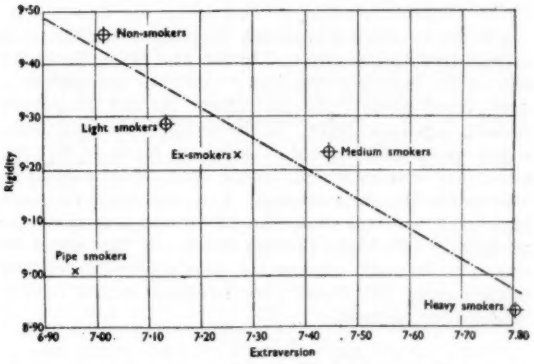
TABLE VI.—*Analysis of Variance Table. Neuroticism and Smoking*

	Degrees of Freedom	Sum of Squares	Mean Squares	Variance Ratio
Between groups ..	3	12·4218	4·1406	0·137
Within ,, ..	1,556	46,998·7323	30·2048	
Total ..	1,559			

P=N.S.

with an increase in numbers significance might be attained, but this is by no means certain.

The results strongly support our hypothesis regarding extraverts being heavier smokers than introverts; they weakly support our hypothesis about non-smokers being more rigid than smokers; they fail to support at an adequate level of significance the hypothesis that smokers



Graph showing relation between smoking habits and rigidity and extraversion.

are more neurotic than non-smokers. A Graph has been prepared to show the relationship between smoking habits on the one hand and rigidity and extraversion on the other. The linearity of regression would seem to lend support to our interpretation of the results.

Discussion

The results of this study support the hypothesis that genotypic personality differences are related to smoking habits. (It should be borne in mind that there is some evidence from twin studies that extraversion is in part determined by genetic factors (Eysenck, 1957), and this personality trait has also been related to certain biological properties of the cortex (Eysenck, 1957.) They do not prove that smoking does not cause lung cancer, but they make more reasonable than had previously been the case the proposition that both smoking and cancer may be causally related to certain underlying genotypic factors. Perhaps the most appealing hypothesis is that extraverts live at an accelerated rate, drinking harder, smoking harder, living more irregular lives, staying up longer, and generally "living it up" more. They may thus (*a*) lower their resistance to disease, and (*b*) expose themselves more to conditions which may directly cause the disease in question. This would agree well with the findings of Pearl (1928) and of Hammond and Horn (1954) that the general death rate among smokers is similar to that of non-smokers of a more advanced age. (It may be that, in addition, non-smokers are biologically self-protective, as Berkson (1958) hypothesizes, and that biologically this is correlated with robustness in meeting mortal stress from disease

generally. Such an additional hypothesis is not strictly necessary, and does not appear very likely to us.)

Some such theory as that outlined above would account for all those features of the evidence which had caused difficulties to the proponents of the "direct action" hypothesis. Inhaling now becomes irrelevant, unless it can be shown to correlate with introversion; it does not provide any obstacle to our theory. The relationship between smoking and non-cancerous diseases also finds an explanation. Lastly, the fact that pipe smokers are not particularly prone to lung cancer finds an easy explanation in terms of their quite different personality structure; a glance at the graph will show that they are even more introverted than are non-smokers. Their failure to develop lung cancer thus finds a much more obvious explanation than the purely *ad hoc* hypotheses to which Fisher (1959) has drawn attention rather scathingly.

Certain consequences follow from these findings with respect to future research. In the first place, the study should be repeated with more extensive questionaries, constructed specifically to follow up the suggestive findings reported above. In the second place, questions ought to be asked about inhaling, in order to test the possibility that introverts inhale more than extraverts who smoke the same amount. Last, and much the most important, a direct study should be undertaken of the personality of victims of lung cancer; if they could be shown to be more extraverted than a carefully chosen control group the theory here advanced would receive considerable support.

Summary

The theory that smoking causes lung cancer has received much support. The investigation here reported was carried out to test certain deductions from an alternative theory, according to which both smoking and lung cancer are symptoms of one and the same underlying factor, related to genotypic differences between smokers and non-smokers. It was hypothesized that cigarette smokers would be (1) more extraverted, (2) less rigid, and (3) more neurotic than non-smokers. An empirical investigation of 2,360 male subjects, selected so as to conform to a predetermined sampling scheme, and stratified according to age, social class, and smoking habits, strongly confirmed the first of these hypotheses, weakly confirmed the second, and failed to confirm the third. Pipe smokers were found to be quite different from cigarette smokers from the point of view of personality, being the most introverted group studied. On the whole the data confirm the view that *genotypic differences exist between smokers and non-smokers, and between cigarette smokers and pipe smokers.*

APPENDIX

5a. Do you find you have to take care of your health or have you a naturally strong constitution? Just say "yes" or "no" to all these points, whichever you think correct. You need not think deeply about it.
b. Do you use up more energy than the average person in getting things done?
c. Do you sometimes feel happy, sometimes depressed, without any apparent reason?
d. Do you prefer action to planning for action?
e. Do you get excited when you argue?
f. Are you inclined to be moody?
6a. Now, can you relax easily when sitting or lying down?
b. Do you become so much absorbed in whatever you're doing that you don't like to be interrupted and have to change to something new?
c. Do you easily show it when you feel sympathy, delight, sorrow, or anger?
d. And if you are feeling angry, sympathetic, or jealous, do you sometimes do things that you regret later on?
e. Are you easily startled when things happen unexpectedly?
f. Would you rate yourself a lively individual?
g. Do you usually take the initiative in making new friends?
h. Are you sometimes bubbling over with energy and sometimes very sluggish?
7a. Do you feel you can really enjoy yourself with friends when you've done your duty and finished whatever task you have in mind?
b. Do you remain outwardly calm when people around you are moved and excited?
c. Does your mind often wander when you are trying to concentrate?
d. Do you have frequent ups and downs in mood either with or without apparent cause?
e. Before going on a trip do you always plan well in advance, decide how you're going and what you're going to do and then feel reluctant to make changes?
f. Would you be very unhappy if you were prevented from making numerous social contacts?
g. Do you get so excited that you use your hands when you talk?
h. Do you suffer from frequent sleeplessness?
8a. Are you easily upset when you're disturbed in something you're concentrating on?
b. Are you happiest in some scheme that calls for rapid action?
c. Do you ever get a lump in your throat when you read a sad story or see an emotional film?
d. Are you frequently lost in thought, even when you're supposed to be taking part in a conversation?
e. Do you think a person who does not live up to the standards he sets himself does not deserve sympathy?
f. Do you always prefer the familiar, the safe and sure, to taking chances with the new and untried?
g. And do you have any habits like chewing pencils or biting finger-nails or things like that?
h. Are you inclined to be quick and sure in your actions?
i. Finally, do you feel one should never take the second-best and only buy the most solid or lasting things are else go without?

REFERENCES

Berkson, J. (1958). *J. Amer. statist. Ass.*, **53**, 28.
Doll, R., and Hill, A. B. (1952). *Brit. med. J.*, **2**, 1271.
—— —— (1954). Ibid., **1**, 1451.
—— —— (1956). Ibid., **2**, 1071.
Eysenck, H. J. (1947). *Dimensions of Personality*. Kegan Paul, Trench, Trubner, London.
—— (1952). *The Scientific Study of Personality*. Routledge and Kegan Paul, London.
—— (1957). *The Dynamics of Anxiety and Hysteria*. Routledge and Kegan Paul, London.
—— (1959). *Manual of the Maudsley Personality Inventory*. Univ. of London Press.
—— (1960a). *The Structure of Human Personality*, 2nd ed. Methuen, London.
—— (Editor) (1960b). *Experiments in Personality*, 2 vols. Routledge and Kegan Paul, London.
Fisher, R. A. (1959). *Smoking—the Cancer Controversy*. Oliver and Boyd, Edinburgh.
Hammond, E. G., and Horn, D. (1954). *J. Amer. med. Ass.*, **155**, 1316.
McArthur, C., Waldron, E., and Dickinson, J. (1958). *J. abnorm. soc. Psychol.*, **56**, 267.
Mass-Observation (1959). *Personality Factors and Smoking*. Mass-Observation, London.
Nigniewitzky, R. D. (1955). *A Statistical Study of Rigidity as a Personality Variable*. Univ. of London: Unpublished thesis.
Pearl, R. (1928). *The Rate of Living*. Knopf, New York.
Simpson, W. J. (1957). *Amer. J. Obstet. Gynec.*, **73**, 808.
Stocks, P., and Campbell, J. M. (1955). *Brit. med. J.*, **2**, 923.
Todd, G. F., and Laws, J. T. (1958). *Tobacco Manufacturers Standing Committee, Research Papers*, No. 2.

SUDANOPHILIC DIFFUSE SCLEROSIS ("SCHILDER'S DISEASE") WITH ICTAL ONSET

BY

M. NEWMAN, M.D., M.R.C.P.

AND

W. H. McMENEMEY, D.M., F.R.C.P.

From the Department of Medicine, St. Mary's Hospital, London, and the Department of Pathology, Maida Vale Hospital for Nervous Diseases, London

The finding of extensive disease of the white matter in a man who until six weeks before his death was a successful car-rally driver seems worthy of record.

Case Report

A professional racing driver and garage proprietor aged 45 was admitted in deep coma to St. Mary's Hospital, London, on July 19, 1956. The previous evening he had come to London to attend a dinner. He had appeared quite normal, though he had complained that same morning of a headache on waking. At the dinner he had been temperate and apparently well, but at midnight he had telephoned his wife to say that he would not return home until the next day. In the afternoon of that following day he was found lying comatose in his hotel bed.

During the previous year, though he had carried on normally with his business and had driven successfully in several events, he had had four fits, one of grand-mal type: the others consisted of transient loss of consciousness followed by headaches, but further information concerning them and their spacing is not forthcoming. His wife denied that there had been any change in his personality or deterioration in his abilities. In the course of his racing career he had had numerous minor injuries but none severe.

On admission he was noted to be a tall thin man without any obvious injury. He was unrousable, with slow gasping respirations (6 per minute), blood-pressure of 90/70 mm. Hg, flaccid limbs, and complete areflexia. As a possible case of barbiturate poisoning he was treated with bemegride, oxygen, and a noradrenaline drip. Lumbar puncture produced cerebrospinal fluid under pressure, containing 15 lymphocytes per c.mm. and 60 mg. of protein per 100 ml. Barbiturates were not identified in the urine.

The next day he responded to painful stimuli, and became violent when carotid angiography was attempted. The blood-pressure was now 130/85, but respirations were still only 12 a minute. Over the next week his state of consciousness was variable but tended to improve, so that he was able to speak and understand, though he still showed marked lack of attention. For a short period there was a divergent squint, but no obvious visual loss and no other abnormality of the cranial nerves; flaccid weakness of the right arm and leg was present, and spasticity of the left limbs with increased tendon reflexes; plantar responses were flexor. During the third week he deteriorated again, becoming incontinent and uncooperative. The right arm and leg remained weak but were now spastic, and there was an extensor plantar response on this side. He seemed unaware of the right side. It was thought that he had a diffuse lesion, probably inflammatory, involving both hemispheres; other suggestions were of tumour at the hind end of the third ventricle or of basilar artery occlusion.

He was transferred to Maida Vale Hospital, but all attempts to define a localized tumour or vascular lesion proved negative. An E.E.G. was recorded on August 13 when the patient was unresponsive. This showed in all regions irregular delta potentials varying in frequency between ½ c./sec. and 3 c./sec. and with an amplitude of 100–200 μV. No persistent focus was demonstrated. Superimposed on the slow rhythms were some low-voltage faster potentials, mainly at 12–18 c./sec. The E.E.G. was considered to be indicative of severe cerebral disease of undetermined nature but unlikely to be a subacute encephalitis (Dr. H. R. A. Townsend). At this time he had no papilloedema. By August 23, however, he had become inaccessible, with spastic tetraplegia, and had developed bilateral papilloedema with haemorrhages. He died a week later.

Post-mortem Findings

A post-mortem examination (Dr. Frances D. Bosanquet) made seven hours after death revealed the body of a man looking somewhat younger than his stated years. The brain weighed 1,430 g. and showed no evidence of the intracranial pressure having been raised. The vertebral, basilar, and internal carotid arteries and the circle of Willis were devoid of atheroma. Except for the internal carotid artery, these basal vessels were, however, all noted to be rather small, the left posterior cerebral artery, which in this brain arose from the basilar artery, being in fact threadlike. Over the right parietal lobe there was a suggestion of fresh subarachnoid haemorrhage, but elsewhere there was no evidence of bleeding, either old or recent. The skull bones showed no evidence of healed fractures. A general examination disclosed confluent bronchopneumonia of both lower lobes, a flabby myocardium discoloured brown, and a small diverticulum of the duodenum but with no evidence of scarring. There was a minimum of atheroma in the aorta and great vessels and in the coronary arteries. A routine histological examination of organs confirmed the presence of bronchopneumonia and revealed early centrilobular necrosis of the liver. In the pars intermedia of the pituitary there was a small cyst.

The brain, after fixation, showed a congestion of the surface vessels over the convexities, with slight thickening of the leptomeninges. Deep to the right Sylvian fissure the substance of the brain felt rather soft, but the convolutional pattern was everywhere normal and there was no atrophy. When the brain was cut coronally, irregular-shaped and sharply cut-out cavities were noted in the white matter of both frontal and occipital lobes (Fig. 1); they tended to

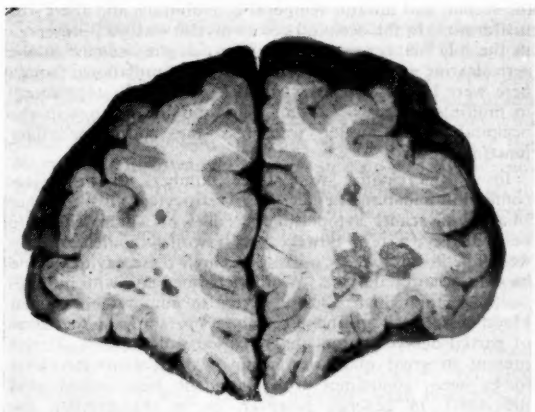


FIG. 1.—Section through frontal lobes of fixed brain to show cavities in white matter.

be symmetrically disposed and there was a suggestion in their pattern that some had been formed as a result of a confluence of small ones. The white matter of the centrum semiovale was generally softer than normal, and in places it appeared to be a little opaque. Plaques of the type seen in multiple sclerosis were not noticeable in the unstained slices.

The brain was studied in frozen, paraffin, and celloidin preparations, the following stains being employed: haematoxylin and eosin, haematoxylin and van Gieson, Mallory's

phosphotungstic acid haematoxylin, Heidenhain, Nissl, Luxol blue, Scharlach R, Holzer, Nile blue, Cajal, Penfield-Cone, Bielschowsky, Davenport, and Glees.

The myelin sections showed extensive pallor of the white matter, notably in the frontal (Fig. 2), occipital, and temporal lobes, and in the central white matter. This pallor tended to be symmetrical, and, while it sometimes impinged on to the central grey matter, the subcortical arcuate fibres were spared and stood out prominently, in great contrast to the subjacent pallor. In general the white matter of the occipital lobes and of the anterior part of the frontal lobes showed a greater loss of myelin than did the parietal lobes and the posterior parts of the frontal lobes, but in these latter areas the loss was greater towards the centre than peripherally. The cavities already noted stood out prominently in the myelin preparations as areas of complete demyelination.

FIG. 2.—Left frontal pole stained for myelin to show widespread general loss but with preservation of the subcortical arcuate fibres. In the areas of softening there is no myelin at all. Heidenhain's stain for myelin. Celloidin at 30 μ.

In the internal capsules an occasional area of complete demyelination could be seen, but for the most part they were intact and there were no patches of partial demyelination. There was slight demyelination in the corpus callosum just anterior to the splenium and mostly on the right, but none in the optic tracts or optic nerves. The white matter of the hippocampal gyrus and of the first temporal convolution on each side was well preserved in comparison with that of the second and inferior temporal convolutions and the gyrus fusiformis. In the occipital cortex myelin was well preserved in the "U" fibres surrounding the calcarine sulcus, in the pericalcarine white matter, and in the optic radiations, though here were to be seen a few small lesions of the type found in multiple sclerosis. At no place did the cavities in the occipital white matter transgress the cortico-medullary junction.

Inside the cavities were large numbers of histiocytes containing sudanophilic fat: also astrocytes, mostly rather small, with scanty cytoplasm the edges of which tended to be concave ; a few, however, had swollen bodies. Fibres were few in number. Coursing through these cavities could be seen occasional axons, mostly deformed and with bulbous swellings upon them. There were also innumerable slender blood-vessels, all of them seemingly patent. In the areas of partial demyelination phagocytosed sudanophilic fat was present in great quantities, while swollen astrocytes were to be seen, sometimes with abundant well-formed glial processes: in general, however, as in the cavities, the astrocytes were rather small, their nuclei being not prominent and their processes indefinite. There were many more intact axons in this part of the white matter than in the completely softened areas: in fact, it appeared that the axons were little disturbed by this demyelinating process. At the cortico-medullary junction the astrocytes were hypertrophied and provided something of a glial wall. In one or two situations, notably in left F.1, F.2, and F.3 posteriorly, this gliosis was, in Holzer sections, visible to the naked eye.

Within the partially demyelinated areas in the frontal lobe could be seen, in addition to the major areas of softening, irregularly defined patches of more intense myelin loss, sometimes with occasional accentuation of the surviving myelin at the periphery of these paler areas. While very often a vessel could be seen in or near the centre of these areas of demyelination, sometimes one noted a ring of relative myelin preservation around a blood-vessel (Fig. 3), a feature which was especially evident immediately adjacent to the cortico-medullary junction. Exceptionally there was endarteritis, but, in general, vessels were not thickened; neither was there any necrosis of vessel walls.

Some of the blood-vessels were cuffed with lymphocytes and histiocytes, but very few fat-filled histiocytes seemed to have gravitated to the perivascular spaces. Eosinophils and plasma cells were not noted. The oligodendroglia were reduced in numbers and in the white matter were confined to the areas which showed little or no demyelination: here they presented no unusual features. They were virtually absent from the areas of complete demyelination, but when present were often surrounded by a halo, while occasionally the nuclei had swollen to such an extent as to make it difficult to distinguish them from those of astrocytes. The cortex appeared normal, except in the posterior part of the right calcarine fissure, where there was a laminar necrosis.

In an adjacent part of the calcarine cortex two penetrating arterioles were seen, associated with a slender surround of softened cortex (Fig. 4). Near to the point of entry of one

FIG. 3.—White matter of left frontal lobe to show patchy nature of demyelination with survival of myelin around many of the blood vessels. Heidenhain's stain for myelin. (×35.)

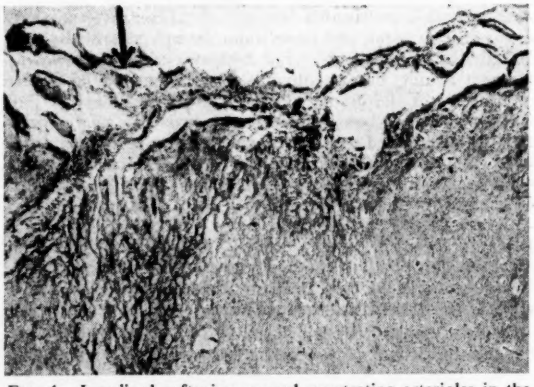


FIG. 4.—Localized softening around penetrating arterioles in the right calcarine cortex. There is a solitary thickened arteriole in the leptomeninges. See arrow. Haematoxylin and eosin stain. (×42.)

of them there was a small grossly thickened but not occluded arteriole in the leptomeningeal space, which it was felt had, because it was thickened, been predisposed to relative stagnation and eventual occlusion: in short, the infarction was believed to be a secondary phenomenon due to the fact that the vessel led into an area of disease characterized by fatty degeneration and general swelling of white matter. The only abnormality in the medulla was a small collection of glial cells in the fasciculus cuneatus. The cerebellum, pons, and spinal cord were normal.

Discussion

The histological findings are in keeping with what is now generally called sudanophilic diffuse sclerosis. Its relationship to multiple sclerosis is uncertain, but some authors (Kufs, 1931; Heernu *et al.*, 1945; Lhermitte, 1950; Lumsden, 1950; Poser, 1957) regard them as variants of the same disease, for many cases of "Schilder's disease" have been recorded which have shown characteristic plaques of multiple sclerosis (such instances have been called "transitional sclerosis" by Poser). When, however, the lesions are confined to the cerebrum and are diffuse in nature, and when the characteristic clinical features of multiple sclerosis and especially its relapsing nature are lacking, then it seems appropriate to speak of the disease as diffuse sclerosis.

The histological findings in the present case, which indicate at least two episodes in the evolution of the process, are believed to be compatible with a total duration of as little as five weeks, and they are comparable with certain cases in the literature to which reference is made below. In view, however, of the history of the fits, a well-recognized early symptom of Schilder's disease, more especially in younger people, the likelihood of some pathological process existing throughout the 12 months cannot be excluded. In this connexion the presence of the subcortical Holzer-positive gliosis might be thought to indicate a chronic process, but it has to be remembered that on occasion it may be met with in as little as one month after the onset of post-traumatic oedema of the white matter (Klatzo *et al.*, 1958) and after a severe anoxic episode (W. Krücke, 1959, personal communication).

The usual course of this condition is a steady march of symptoms characterized by mental deterioration with blindness or spastic paralysis, progressing to coma and death in a period of 3 to 12 months. Headache is frequent, and transient attacks of unconsciousness may occur; ocular symptoms are almost always complained of, and swelling of the optic-nerve head is common. In some cases the onset is acute, and the course more rapid.

Bouman (1934) collected details of 94 cases, four of these patients having died in under one month from the onset of symptoms. Of the recorded instances with rapid evolution and with histological changes of a comparable order the following may be epitomized. Case 3 of Stewart *et al.* (1927) was a woman aged 43 in whom sudden blindness in both eyes was apparently the first symptom eight days before death. The brain showed acute swelling of the astrocytes but with little fibre formation except in the occipital areas, and then only in relation to vessels. Sheldon *et al.* (1929) reported rapidly developing focal symptoms with raised intracranial pressure in a 27-year-old woman who six and a half weeks previously had given birth to her first child, to be followed first by puerperal sepsis lasting three weeks and then by blindness which developed over a period of one week. The true nature of the disease became manifest during craniotomy. Necropsy four days later disclosed marked demyelination of the left occipital lobe with preservation of the "U" fibres and local involvement of the corpus callosum and right temporo-parietal and occipital lobes with implication of the arcuate fibres on this side. There was extensive destruction of axis cylinders.

In Case 1 of Bini and Spaccarelli (1947) the patient, a boy of 9, became paralysed and demented in a week from the onset of symptoms. The distribution of the lesions was not dissimilar from the case we have described but the emphasis of destruction was in the occipital regions. There was a general weak staining of the myelin noticeable almost everywhere, though the "U" fibres were spared. A few islets of preserved myelin were noted and also confluent halos of demyelination around vessels. Axis-cylinder loss was not as marked as the loss of myelin. There was some perivascular infiltration with lymphocytes and also small perivascular bleedings, not necessarily in the areas where the pathological process was to be seen. The astrocytes showed moderate hypertrophy, fibre formation in the Holzer prepration being described as "very modest."

Környey (1952) described the case of a woman aged 21 who became somnolent eight days after a cold and five days after the appearance of an urticaria-like rash, lapsing into coma and dying seven days later. The lesions anteriorly were diffuse and massive, but posteriorly they were multiple. The demyelination was uneven and not always complete, the most defective areas being centred around small blood vessels. The author describes some loss of axis-cylinders and spindle-like swelling on others, with lymphocytes and plasma cells cuffing vessels, and moderate hypertrophy and hyperplasia of the neuroglia. Braitenberg and Callieri (1955) report an illness of 12 days' duration in a boy aged 13 with dementia and bulbar signs. A large subcortical lesion was found in the right frontal lobe, but the medulla was not examined.

The present case is therefore another example of the disease exhibiting a rapid evolution, but the lapse into coma in so few hours would appear to be exceptional. The ictal onset in a man of this age had naturally in life suggested the presence of a cerebrovascular lesion, and when the destruction of white matter was noted the diagnosis of Binswanger's (1894) disease was considered. The finding of two disordered transcortical arterioles in the occipital lobes with softening of the contiguous grey matter lent some support to this suggestion, but a more detailed study failed to demonstrate any of the thickening of the arterioles in the white matter which has been noted by those who have reported such cases (Nissl, 1920; Grünthal, 1929; Farnell and Globus, 1932; Davison, 1942; and Pilleri and Risso, 1959). Neumann (1947) is of the opinion that some cases of reported Binswanger's disease may be no more than instances of Schilder's disease occuring in arteriosclerotic subjects. The very occasional thickening of the blood-vessels noted in the present case was believed to be secondary to the stasis and to the accumulated products of myelin breakdown.

Åström *et al.* (1958) have described an unusual form of demyelination in two patients with chronic lymphatic leukaemia and in one case of Hodgkin's disease in which the nuclei of the oligodendrocytes were frequently swollen and densely basophilic and those of the astrocytes were markedly hyperchromatic and irregular. The distribution of lesions in these brains was not so typical of Schilder's disease as in the present case, and

the unusual changes they described in the astrocytes were not found by us. Christensen and Fog (1955) have reported a case of Schilder's disease in a 59-year-old man whose illness lasted five months and was associated with sarcoidosis of the lungs, spleen, lymph nodes, and kidney; and they advance the suggestion that both the cerebral and the systemic diseases may have been co-ordinated allergic reactions. When the sarcoidosis was treated with A.C.T.H. the brain disease progressed rapidly, but the possibility of coincidence could not be excluded. They believe that the primary lesion in the brain was a degeneration of the oligodendroglia.

In the present case the paucity of oligodendrocytes in the affected parts was striking, but on histological grounds it is not possible to say whether their dissolution preceded or followed that of the myelin. The demyelination which follows cyanide intoxication may, however, be due to a derangement of enzyme activity in the oligodendrocytes (Lumsden, 1950), so it is reasonable to suppose that a similar mechanism may obtain in certain other forms of demyelinating disease. In the present case, apart from the unexplained early centrilobular necrosis of the liver, there was no evidence of intoxication, anoxia, or infection, but the history of fits and blackouts is consistent with recurrent "allergic" episodes of a functional character, preceding the acute destructive process in the brain. Myelin preservation noted in this case around some of the vessels in the central zone has been previously reported by Meyer and Pilkington (1936).

In general, demyelination seemed to occur most in the areas of late myelinogenesis; thus demyelination was pronounced in the frontal lobes and the middle and inferior temporal gyri, whereas the first temporal and hippocampal gyri were spared. But the diffuse involvement of the occipital lobe proved to be an important exception to this generalization, though the relative integrity of the pericalcarine white matter, apart from the few small and young plaques, was noteworthy.

Summary

A case of demyelinating disease of the brain in a man of 45 years presented with an apoplectic onset, followed by fluctuating signs of bilateral cerebral disorder and ending in death after a total period of six weeks.

The brain showed diffuse, irregular cavitation of the white matter, with extensive patches of demyelination, sparing the subcortical arcuate fibres. The histological changes were those of sudanophilic diffuse sclerosis, a condition usually associated with a slowly progressive clinical course.

Reference is made to other acute cases in the literature.

We are grateful to Professor W. S. Peart and to Mr. Valentine Logue for access to their case notes, and to Dr. Frances D. Bosanquet, who carried out the necropsy. We also thank Mr. G. Cox and Miss M. Doe for their technical assistance.

REFERENCES

Aström, K. E., Mancall, E. L., and Richardson, E. P., jun. (1958). *Brain*, **81**, 93.
Bini, L., and Spaccarelli, G. (1947). *Riv. Neurol.*, **17**, 362.
Binswanger, O. (1894). *Berl. klin. Wschr.*, **31**, 1180.
Bouman, L. (1934). *Diffuse Sclerosis*, p. 150. Wright, Bristol.
Braitenberg, V., and Callieri, B. (1955). *Riv. Neurol.*, **25**, 771.
Christensen, Erna, and Fog, M. (1955). *Acta psychiat. scand.*, **30**, 141.
Davison, C. (1942). *J. Neuropath. exp. Neurol.*, **1**, 42.
Farnell, F. J., and Globus, J. H. (1932). *Arch. Neurol. Psychiat. (Chicago)*, **27**, 593.
Grünthal, E. (1929). *Arch. Psychiat. Nervenkr.*, **88**, 849.
Heernu, J., Martin, P., and Van Bogaert, L. (1945). *Mschr. Psychiat. Neurol.*, **110**, 68.
Klatzo, I., Piraux, A., and Laskowski, E. J. (1958). *J. Neuropath. exp. Neurol.*, **17**, 548.
Környey, S. (1952). *A.M.A. Arch. Neurol. Psychiat.*, **68**, 683.
Kufs, H. (1931). *Arch. Psychiat. Nervenkr.*, **93**, 564.
Lhermitte, F. (1950). *Les Leuco-encéphalites*. Flammarion, Paris.
Lumsden, C. E. (1950). *J. Neurol. Psychiat.*, **13**, 1.
Meyer, A., and Pilkington, F. (1936). *J. ment. Sci.*, **82**, 812.
Neumann, Meta A. (1947). *J. Geront.*, **2**, 57.
Nissl, F. (1920). *Z. Neurol. Psychiat.*, **19**, 438.
Pilleri, G., and Risso, M. (1959). *Psychiat. et Neurol. (Basel)*, **137**, 209.
Poser, C. M. (957). *J. Neuropath. exp. Neurol.*, **16**, 61.
Schilder, P. (1912). *Z. ges. Neurol. Psychiat.*, **10**, 1.
Shelden, W. D., Doyle, J. B., and Kernohan, J. W. (1929). *Arch. Neurol. Psychiat. (Chicago)*, **21**, 1270.
Stewart, T. G., Greenfield, J. G., and Blandy, M. A. (1927). *Brain*, **50**, 1.

GIANT FOLLICLE LYMPHOMA OF THE SPLEEN

RECOVERY AFTER SPLENECTOMY

BY

R. A. HICKLING, B.A., M.D., F.R.C.P.

Physician, Charing Cross Hospital, London

This paper is concerned with four patients with the following features: (1) Massive splenomegaly without enlargement of superficial lymph nodes. (2) Lymphocytosis without any great increase in total leucocytes, and with the presence of abnormal and immature mononuclear cells in the circulating blood. (3) Large numbers of lymphocytes in bone-marrow aspiration films. (4) In the two cases in which bone-marrow biopsy was carried out there were numbers of lymphocyte foci in active marrow. (5) Excellent clinical result of splenectomy. (6) In the course of time the abnormal and immature mononuclear cells in the circulating blood disappeared and the leucocyte count returned to normal, the lymphocytosis disappearing. (7) In the three cases in which liver biopsy was carried out at the time of splenectomy there were abnormal lymphocyte accumulations in the portal tracts. (8) No superficial lymph-node enlargements occurred during the periods of observation, and the patients remained well (one patient died of pneumonia 13 years after splenectomy and no sign of any lymph-node disease was found at necropsy).

The histological appearances of the spleens in Cases 1 and 2 were typical of giant follicle lymphoma, and the lymph nodes which were removed with the spleens showed the same histological changes. In the spleens in Cases 3 and 4 the follicles were large and ill-defined; there were large numbers of lymphocytes and lymphoblasts in the splenic pulp, and the histological appearances were thought to be those of lymphosarcoma or lymphatic leukaemia. However, these two cases were exactly similar in all other respects to Cases 1 and 2 with regard to symptoms, signs, response to splenectomy, and subsequent progress, and this, together with the known close relationship of giant follicle lymphoma to lymphatic leukaemia and to lymphosarcoma, indicates that the same disease process was present in all four cases. Summaries of the four cases follow.

Case 1

A woman aged 34 was first seen in September, 1952, with lack of energy for 18 months and increasing abdominal swelling for two months. The spleen reached to the midline and half-way between the umbilicus and the symphysis pubis. There was no anaemia. Leucocytes numbered

10,000–15,000/c.mm., of which 75 to 80% were lymphocytes with 2 to 9% of immature and abnormal mononuclear cells. Sternal puncture in 1952 and 1953 showed predominantly lymphatic bone-marrow. *X*-ray therapy to the spleen in September, 1952, and January to February, 1953, produced some diminution in the size of the spleen and some improvement in general health, but only for a few weeks. In October, 1953, a course of nitrogen mustard intravenously had only a temporary effect, both on the size of the spleen and on general health. Both *x*-ray therapy and nitrogen mustard produced transient leucopenia. Splenectomy in February, 1954, brought an excellent clinical response. Her general health improved rapidly and the circulating blood gradually returned to normal, the percentage of lymphocytes and the numbers of immature and abnormal mononuclear cells diminishing, so that by February, 1955, one year after the splenectomy, the total and differential leucocyte counts were normal and no abnormal cells were seen. The patient has been seen and her blood examined every few months since. At the time of writing, five and a half years after splenectomy she remained well, had developed no enlarged lymph nodes, and her blood count was normal. At operation, liver biopsy was carried out, the sections showing large accumulations of lymphocytes in the portal tracts, similar to those in cases of lymphatic leukaemia. Enlarged lymphatic glands were found in the hilum of the spleen, and many elsewhere in the abdomen. No attempt was made to remove them, except those which came away with the spleen and which showed the appearances of giant follicle lymphoma.

Case 2

A woman aged 43 first seen in April, 1956, on account of a thrombosis of the central artery of the retina of the left eye. For four months she had had abnormal tiredness, colicky abdominal pains, and diarrhoea with a feeling of pressure across the upper part of the abdomen. The spleen extended ¾ in. (2 cm.) beyond the midline and to half-way between the umbilicus and symphysis pubis. There was a mild anaemia, the haemoglobin being 73%, and the leucocytes numbering 5,000/c.mm., of which 61% were leucocytes, 4 being immature and abnormal. In August and September, 50 to 60% of the leucocytes were lymphocytes, several being immature and abnormal. Sternal-puncture films revealed large numbers of lymphocytes. Bone-marrow biopsy showed several lymphocyte foci in an active marrow. She had three courses of deep *x*-ray treatment to the spleen—in August and September, 1956, and in March and October, 1958. Each of these caused some decrease in the size of the spleen and improvement in general health, but the effect lasted only a few weeks on each occasion. During all this time more than half the circulating leucocytes were lymphocytes, and in all films immature and abnormal lymphocytes were seen in varying proportions.

Splenectomy was carried out in April, 1959, with bone-marrow biopsy, liver biopsy, and removal of large lymph nodes in the hilum of the spleen. The clinical result was excellent; all symptoms disappeared, and in August, four months after splenectomy, she felt quite well, and had no anaemia and no enlarged glands. Bone-marrow biopsy sections showed numbers of lymphocyte foci in active bone-marrow, liver biopsy sections revealed lymphatic accumulations in the portal tracts, and the lymph nodes in the hilum of the spleen showed the changes of giant follicle lymphoma. Many other enlarged lymph nodes were felt in the abdomen at operation, but no attempt was made to remove them. The circulating blood still contained a few abnormal and immature mononuclear cells in August, 1959, but the lymphocytosis had disappeared.

Case 3

In 1938, during routine examination of a woman aged 67 for some trivial illness, an enlarged spleen was found. The splenomegaly produced no symptoms until 1942 when she noticed tightness in the left side of the abdomen, constipation, and loss of weight. At that time the spleen extended to half-way between the umbilicus and the symphysis pubis. Blood examination showed very mild anaemia, normal numbers of leucocytes, lymphocytes varying between 68 and 82% with many immature and abnormal forms, and diminished numbers of platelets. Sternal-puncture films showed that almost all the cells were lymphocytes or lymphoblasts. She developed ascites and oedema of the sacrum and legs. In October, 1943, splenectomy was carried out. The result was excellent, and the ascites and peripheral oedema disappeared. During the next few years she developed arterial hypertension and mild polycythaemia, and had several cerebral vascular accidents from which she made good recoveries; she finally died of pneumonia in February, 1957, aged 86, 13½ years after splenectomy. At necropsy no sign of any lymphatic disease was found. The liver contained no lymphatic accumulations, and two lymph nodes from different parts of the body showed no sign of disease.

The abnormal circulating blood persisted until May, 1952, nine years after splenectomy. During this time the total leucocytes were normal, but there was a lymphocytosis at almost every examination, with a few abnormal and immature mononuclear cells. By October, 1952, the total and differential leucocyte count had become normal and remained so in 1953, 1954, and 1955. No count was made in 1956. The histological examination of the spleen showed large irregular follicles composed mainly of lymphoblasts, and there were many lymphocytes and lymphoblasts in the splenic pulp.

Case 4

A man aged 51 was first seen in May 1958, complaining of excessive tiredness. His doctor found moderate anaemia and a large spleen extending to 1½ in. (3.8 cm.) beyond the midline and to half-way between the umbilicus and the symphysis pubis. Haemoglobin was 60%; white cells numbered 9,700, of which 80% were lymphocytes. The patient had first noticed abdominal discomfort, with a feeling of hardness in February, 1957. In August, 1958, the leucocytes were 8,000–10,000/c.mm., lymphocytes 82 to 84%, with 2 to 11% of immature and abnormal mononuclear cells. Sternal-puncture films showed an excess of lymphocytes. Bone-marrow biopsy revealed many lymphatic foci in an active marrow. *X*-ray treatment to the spleen in August, 1958, made him feel more comfortable; but it brought little change in the size of the spleen, and the haemoglobin fell to 35%. He was given a blood transfusion and sent home. He was readmitted in October because of profound weakness. He had severe anaemia; the leucocytes remained as before. Blood transfusion was followed by splenectomy on October 22. Improvement was rapid, and he left hospital well in November. He remained well, with no anaemia and no enlarged lymph nodes, up to September, 1959, 11 months after splenectomy.

In this case the circulating blood has not yet become quite normal, though there is a steady change towards this. In September, 1959, the lymphocytes numbered 46%, with 2% immature and abnormal mononuclear cells. Liver biopsy carried out at operation showed accumulations of lymphocytes in the portal tracts. Large lymph nodes were present in the hilum of the spleen; these were removed with the spleen. The spleen and lymph nodes contained very large ill-defined lymphatic follicles, with lymphocytic accumulations in the pulp. Many other enlarged lymph nodes were felt and seen elsewhere in the abdomen, but no attempt was made to remove them.

March, 1960.—Cases 1, 2, and 4 remain well in every way, with normal total and differential leucocyte counts, but in Cases 2 and 4 a very few abnormal and immature mononuclear cells persist in the circulating blood.

The Literature

Giant follicle lymphoma (follicular lymphoma; Brill–Symmers disease) is a disease of the lymph nodes, both

superficial and deep, but in a high proportion of cases the spleen is affected and is consequently enlarged. In reviews of large numbers of cases the spleen was enlarged in 64% (Symmers, 1938), in 33% of 63 cases (Gall *et al.*, 1941), 39% of 208 cases (Wetherley-Mein *et al.*, 1952), 42% of 275 cases (Bilger, 1954), and 49% of 253 cases (Rappaport *et al.*, 1956). But cases with splenomegaly but without enlargement of superficial lymph nodes appear to be rare. Bilger (1954) in his very comprehensive review says that there are cases in which the spleen is the only organ affected. I have been able to find references to only 14 cases. Three probable cases were described by de Jong (1921) and one each by Ferrata and Introzzi (1933), McNee (1934), Decker and Little (1935), Sherwin and Spirtes (1940), Symmers (1942), Fischer (1942), Israëls (1953), Ravina *et al.* (1954), Reymond and Gonin (1954), Cantoni and Massari (1955), Varró and Kelemen (1958). Of these, two died shortly after the operation, one two years after operation. In three cases lymph nodes became involved later (Sherwin and Spirtes, 1940; Decker and Little, 1935, 1957; Varró and Kelemen, 1958), and in one the patient became ill again four months after splenectomy though enlarged glands did not appear (Ravina *et al.*, 1954). Chevallier (1956) performed splenectomy on five patients presenting with multiple haemorrhages in which the spleens showed the changes of giant follicle lymphoma; two died within a few days and the three survived soon developed haemorrhages again. The spleens were not large, and these cases probably do not belong to the group considered here.

In the other cases splenectomy had been performed for diagnostic purposes, because of symptoms caused by the size of the spleen, or because of the belief that the spleen was interfering with the proper functioning of the bone-marrow ("hypersplenism"). Varró and Kelemen (1958) carried out splenectomy on a patient who was well two and a half years later but then developed neck glands, and they collected from the literature 26 cases of giant follicle lymphoma in which splenectomy had been carried out. Rappaport *et al.* (1956) reported that splenectomy had been done in 8 of their 253 cases. In a disease which may last for very many years and which may cause the death of the patient without change in histological pattern (Cohen and Bergstrom, 1946), or which may cause the patient's death through a change into lymphosarcoma or lymphatic leukaemia, it is very difficult to know what the ultimate effect of splenectomy may be, but most authors regard splenectomy as not curative. For example, Decker and Little (1957), after describing the case of a patient who died, probably of lymphosarcoma, 2½ years after splenectomy, say "there is no reason to believe that splenectomy is helpful or is indicated as a therapeutic measure." They carried out the operation as a diagnostic measure and to relieve abdominal symptoms. Bilger (1954), in his comprehensive review of 275 cases, found that splenectomy had been carried out in 20, and states that a cure was never obtained.

Blood Picture

All those who have reviewed large numbers of cases of giant follicle lymphoma comment on the variability of the blood picture. There is usually a slight anaemia. Most cases have a normal total and differential leucocyte count. But in some a relative or absolute lymphocytosis is described, and in a few the blood picture of lymphatic leukaemia (Klemperer, 1934; Symmers, 1938; Anday and Schmitz, 1952; Rosenthal *et al.*, 1952; Wright, 1956). Only 6 of the 208 cases reviewed by Wetherley-Mein *et al.* (1952) had "anomalous white blood counts." Some cases have leucopenia with relative lymphocytosis, some have lymphocytosis or monocytosis, and some have an eosinophilia (Bilger, 1954).

Abnormal Cells in the Circulating Blood

"In rare cases there are unripe lymphocytes or unclassifiable cells in the blood" (Bilger, 1954). Abnormal cells in the circulating blood have often been described (de Jong, 1921; Ross, 1933; Mallory, 1935; Mayer and Thomas, 1939; Baehr and Klemperer, 1940; Salm, 1940; Gall *et al.*, 1941; Gall and Mallory, 1942; Haas, 1956). These cells are variously described as lymphoblasts, immature lymphocytes, abnormal lymphocytes, pathological lymphocytes, atypical monocytes, or atypical cells. More careful examination of the cells in the circulating blood would probably reveal more cases with abnormal cells (Wright, 1956). Rappaport *et al.* (1956) regarded the presence of abnormal lymphocytes in the blood as an indication of leukaemia even though the total leucocytes were within normal limits. Of their 253 cases, 23 had abnormal lymphocytes in the circulating blood.

Many different types of abnormal and immature mononuclear cells have been found in the circulating blood of the four cases described in this paper. Some are lymphoblasts, some are large lymphocytes with kidney-shaped nuclei, others are lymphocyte-like cells with split nuclei, but the most characteristic is a cell in appearance intermediate between a monocyte and a lymphocyte, with a large finely woven nucleus containing several nucleoli.

Bone-marrow

There are not many references to bone-marrow examination in cases of giant follicle lymphoma. Bilger (1954) says the results of bone-marrow puncture are very varied, some workers finding normal marrow, others more or less increase in lymphocytes. Cooper and Watkins (1949) found a slight increase in normal lymphocytes in one case. Berman *et al.* (1950) found numerous lymphocytes of reticular origin. Anday and Schmitz (1952) reported the bone-marrow full of abnormal lymphocytes. Rosenthal *et al.* (1952) found abnormal lymphocytes in the bone-marrow, and Heintzelmann (1946) discovered "reticular cells" in the bone-marrow. In all my cases sternal-marrow contained excessive numbers of lymphocytes in varying degrees. In Case 3 nearly all the cells were lymphocytes and lymphoblasts. The reason for the variation in the numbers found may depend upon the fact that the lymphocytes occur in localized masses and there is an element of chance whether one of these masses would be aspirated by the needle. Several writers have found these masses in the bone-marrow at post-mortem examination (Ross, 1933; Scott and Robb-Smith, 1936; Dameshek *et al.*, 1937; Fischer, 1942; Cohen and Bergstrom, 1946; Pettet *et al.*, 1955).

Cooper and Watkins (1949) made sections of very small portions of bone-marrow removed by needle puncture and in one a localized mass of lymphocytes was found. Heintzelmann (1946) suggested, as a result of bone-marrow puncture examinations, that there probably were follicles of lymphocytes in the bone-marrow. Pettet *et al.* (1955), in an evaluation of paraffin sections of aspirated bone-marrow in malignant lymphomas, found this examination less helpful in the six cases of follicular lymphoma in their series than in

the other groups. They found diffuse infiltrations of lymphocytes in two cases and aggregates of lymphocytes in one case. In 13 of their 72 cases of malignant lymphomas they found benign aggregates of lymphocytes, and in 1,750 bone-marrow examinations for miscellaneous conditions similar aggregates were found in 48. Miale (1958) states that lymphoid nodules are found infrequently in adult marrow but are not uncommon in infants and children.

There are not many records of the findings in the liver in cases of giant follicle lymphoma. Scott and Robb-Smith (1936) found hyperplasia of periportal lymphoid tissue in one case. Rappaport *et al.* (1956), in four cases at needle biopsy of the liver, found follicles in the portal tracts exclusively, and on surgical biopsy showed lymphocytes in the portal tracts and subcapsular regions of the liver. Varró and Kelemen (1958) in their case found needle biopsy negative on two occasions, but liver biopsy at the time of splenectomy revealed lymphocytic nodes in the liver.

Discussion

It is possible that several different disease processes may cause the histological changes of giant follicle lymphoma. This is strongly suggested by the great variations in the circulating blood and in the bone-marrow. The four cases described here may be examples of one such disease process, which may be an example of a primary disease of the spleen, of unknown cause, that alters the balance between the production and destruction of the lymphocytes, causing the abnormal circulating blood and the lymphocyte accumulations in the bone-marrow and liver. Splenectomy restores the normal balance and gradually the circulating blood becomes normal. It is suggested that patients presenting the features enumerated at the beginning of this article belong to a single group. These features do not suggest that the condition is a neoplasm—for example, lymphosarcoma—for the spleens were already massive when first noticed, and had therefore been enlarged for a considerable period, and even then they were observed, respectively, for 17 months, 3 years, 5 years, and 5 months in the four cases before splenectomy. Also, though many enlarged lymph nodes were seen and felt in the abdomen at operation in cases 1, 2, and 4, no attempt was made to remove them, and during the periods of observation they have caused no symptoms or signs.

Nor does the subsequent course of events suggest that the condition is lymphatic leukaemia, for after splenectomy the circulating blood gradually became normal, and has remained so for the periods of observation. The disease process appears to have been stopped. Though the periods of observation after splenectomy in Cases 2 and 4 are of months only, the complete relief of symptoms and the gradual change of the circulating blood towards normal suggests that a "cure" has been effected. Prolonged careful observation of many more cases is needed for this to be proved.

Summary

Four cases are described of an illness characterized by gross splenomegaly without enlargement of superficial lymph nodes and by changes in the circulating blood and in bone-marrow puncture films suggestive of aleukaemic lymphatic leukaemia. All four patients made a good recovery after splenectomy, the symptoms disappearing and the circulating blood gradually returning to normal. There may be several conditions which cause the morbid anatomical appearances and histological changes of giant follicle lymphoma, and the cases here described may be one of these.

All four patients were in Charing Cross Hospital. Dr. N. S. Plummer allowed me to study Case 4. The other three were under my own care. Professor W. St. C. Symmers, professor of morbid anatomy, Charing Cross Hospital Medical School, discussed the sections with me. Dr. F. R. Philps, pathologist to St. Mary's Hospital, Eastbourne, performed the post-mortem examination in Case 3, and sent me sections. Mr. N. C. Lake performed splenectomy upon Cases 1 and 3, and Mr. N. C. Tanner upon Cases 2 and 4. I am grateful to all these for their kind help.

References

Anday, G. J., and Schmitz, H. L. (1952). *A.M.A. Arch. intern. Med.*, **89**, 621.
Baehr, G., and Klemperer, P. (1940). *N.Y. St. J. Med.*, **40**, 7.
Berman, L., Klein, A. A., Linn, H. J., and Bates, G. S. (1950). *Blood*, **5**, 286.
Bilger, R. (1954). *Ergebn. inn. Med. Kinderheilk.*, **5**, 642.
Cantoni, L., and Massari, N. (1955). *Policlinico, Sez. med.*, **62**, 75.
Chevallier, P. (1956). *Sang*, **27**, 841.
Cohen, S. E., and Bergstrom, V. W. (1946). *Amer. J. clin. Path.*, **16**, 22.
Cooper, T., and Watkins, C. H. (1949). *Blood*, **4**, 534.
Dameshek, W., Henstell, H. H., and Valentine, E. H. (1937). *Ann. intern. Med.*, **11**, 801.
Decker, H. R., and Little, H. G. (1935). *J. Amer. med. Ass.*, **105**, 932.
—— —— (1957). Ibid., **165**, 1178.
de Jong, R. de J. (1921). *Beitr. path. Anat.*, **69**, 185.
Ferrata, A., and Introzzi, P. (1933). *Haematologica*, **14**, 159.
Fischer, W. (1942). *Virchows Arch. path. Anat.*, **309**, 795.
Gall, E. A., and Mallory, T. B. (1942). *Amer. J. Path.*, **18**, 381.
—— Morrison, H. R., and Scott, A. T. (1941). *Ann. intern. Med.*, **14**, 2073.
Haas, W. (1956). *Folia haemat. (Lpz.)*, **74**, 65.
Heintzelmann, F. (1946). *Acta med. scand.*, **124**, 359.
Israëls, M. C. G. (1953). *Lancet*, **2**, 525
Klemperer, P. (1934). *Amer. J. med. Sci.*, **188**, 593.
McNee, J. W. (1934). *J. Path. Bact.*, **39**, 83.
Mallory, T. B. (1935). *New Engl. J. Med.*, **213**, 67.
Mayer, S., and Thomas, H. M. (1939). *Bull. Johns Hopk. Hosp.*, **64**, 315.
Miale, J. B. (1958). *Laboratory Medicine—Hematology*. Mosby, St. Louis.
Pettet, J. D., Pease, G. L., and Cooper, T. (1955). *Blood*, **10**, 820.
Rappaport, H. Winter, W. J., and Hicks, E. B. (1956). *Cancer (N.Y.)*, **9**, 792.
Ravina, A., Pestel, M., and Thielen, R. (1954). *Bull. Soc. méd. Hôp. Paris*, **70**, 796.
Reymond, A., and Gonin, P. M. (1954). *Schweiz. Z. allg. Path.*, **17**, 757.
Rosenthal, N., Dreskin, O. H., Vural, I. L., and Zak, F. G. (1952). *Acta haemat. (Basel)*, **8**, 368.
Ross, J. M. (1933). *J. Path. Bact.*, **37**, 311.
Salm, R. (1940). *Edinb. med. J.*, **47**, 486
Scott, R. B., and Robb-Smith, A. H. T. (1936). *St. Bart's Hosp. Rep.*, **69**, 143.
Sherwin, B., and Spirtes, M. (1940). *Ann. Surg.*, **111**, 459.
Symmers, D. (1938). *Arch. Path. Lab. Med.*, **26**, 603.
—— (1942). Ibid., **34**, 385.
Varró, V., and Kelemen, E. (1958). *Folia haemat. (Lpz.)*, **75**, 182.
Wetherley-Mein, G., Smith, P., Geake, M. R., and Anderson, H. J. (1952). *Quart. J. Med.*, **21**, 327.
Wright, C. J. E. (1956). *Amer. J. Path.*, **32**, 201.

The Sir George Earle Trophy for industrial safety has been awarded this year to Associated Electrical Industries (Manchester) Ltd. (formerly Metropolitan-Vickers Electric Co. Ltd.). An accident-prevention committee has been part of the company's safety organization for 34 years, and the frequency rate for reportable accidents has shown a continuous downward trend: during the past 12 years it has fallen from 1.13 to 0.46. The Trophy was presented to the Royal Society for the Prevention of Accidents in 1956 by Sir George Earle for annual award to any firm or organization which had made a meritorious contribution to progress in industrial safety.

ACCIDENTAL ACQUIRED HYPERSENSITIVITY TO TETANUS ANTITOXIN

BY

I. B. SNEDDON, M.B., Ch.B., F.R.C.P.

Consultant Dermatologist, United Sheffield Hospitals

Reactions to tetanus antitoxin are a familiar problem to casualty officers, but it must be very unusual for a casualty officer to develop symptoms merely from handling this serum. It has not been possible to discover any account of such reaction in the literature, but in the following case it does seem to have occurred.

In an attempt to confirm the diagnosis, the trial dose of tetanus antitoxin recommended for allergic subjects (Laurent and Parish, 1952; Parish, 1958) was injected subcutaneously and produced a severe and prolonged allergic reaction.

Case Report

A 23-years-old woman casualty officer noticed that after giving a patient an injection of tetanus antitoxin she had slight swelling of the eyelids with some conjunctival injection. Two days later she gave three injections of tetanus antitoxin in the early hours of the morning. By 5.45 a.m. she had quite severe oedema of the eyelids and was sent off duty. Apart from the swelling of the eyelids, she felt well.

I saw her the next afternoon, and from her history a possible exogenous cause for the urticarial swelling of the eyelids, which was still present, was thought to be the contact with tetanus antitoxin. She admitted that she held the syringe up at eye level and expressed antitoxin through the needle to get the correct dose. It was therefore possible for the serum to have reached her conjunctiva by air-borne droplets. She gave no personal or family history of allergic disease.

Some years previously she had been immunized with tetanus toxoid. This is a mild prophylactic which does not contain horse protein or anything else likely to cause sensitization. She had never had serum, nor had she been immunized against diphtheria. The possibility of injections of diphtheria prophylactic, T.A.F., which contains a small amount of horse serum, was excluded.

On examination there was urticarial swelling of her eyelids with no scaling to suggest epidermal damage. In order to confirm the presumptive diagnosis, she was given 0.2 ml. of a 1 in 10 dilution of tetanus antitoxin intradermally into the right forearm at 3.30 p.m. on October 16, 1959. A weal and flare 4 by 1 in. (10 by 2.5 cm.) developed in 10 minutes, and five minutes later her nose began to run and she started to cough. Five minutes later she became very distressed and developed acute bronchospasm. Her colour remained good and there was no evidence of vasomotor collapse. She was given 0.3 ml. of 1 in 1,000 adrenaline subcutaneously and admitted to the ward for observation, though her asthma was subsiding.

On admission at 4 p.m. she was given 8 mg. of chlorpheniramine maleate orally. At 4.45 p.m. an acute generalized urticarial eruption appeared, and in half an hour she complained of epigastric pain and vomited repeatedly. Another 0.3 ml. of 1 in 1,000 adrenaline was given, but she continued to vomit, and later the same evening she became more wheezy and complained of a feeling of constriction in the retrosternal region. By 11.50 p.m. she was collapsed and dyspnoeic; the urticaria was intense, and by this time had involved her lips and throat. The most distressing symptom was the repeated vomiting. Hydrocortisone succinate, 100 mg. given intravenously, brought some improvement in 30 minutes. By 2.15 a.m. on October 17 she was again worse, and another 100 mg. of hydrocortisone was given intravenously. At 5 a.m. 100 mg. of hydrocortisone and 10 mg. of chlorpheniramine maleate were given intramuscularly.

During the morning she appeared better, and treatment was changed to intramuscular prednisolone and chlorpheniramine maleate 10 mg. every three hours. By this time it was hoped that the worst was over.

At 4 p.m., however, she developed another and more severe attack of urticaria, vomiting, and asthma. Her blood-pressure fell to 75/50. She had not passed urine for 20 hours, and the possibility that she had developed anuria was considered; but she was encouraged to try to pass urine, and did pass 13 oz. (840 ml.), which contained no abnormal constituents. Blood taken at this time showed a urea content of 54 mg./100 ml. and normal electrolytes.

The patient was naturally very alarmed, and treatment was changed again to hydrocortisone, 100 mg. three-hourly, chlorpheniramine maleate, 10 mg. six-hourly, together with intramuscular sodium phenobarbitone, 3 gr. (0.2 g.) every eight hours.

She slept fairly well, but at 11.30 a.m. on October 18 her condition again gave anxiety with a recurrence of vomiting, urticaria, and asthma. This passed off after an additional dose of 100 mg. of hydrocortisone intramuscularly had been given. The regime of hydrocortisone, 100 mg. three-hourly, chlorpheniramine maleate, 10 mg. six-hourly, and sodium phenobarbitone, 3 gr. (0.2 g.) eight-hourly, was continued.

On October 19 she was much improved—only a residual urticarial patch on the site of the injection to her forearm remained. Treatment was changed to cortisone, 50 mg. t.d.s., and chlorpheniramine maleate, 8 mg. t.d.s.; the cortisone was lowered steadily until October 22, when it was discontinued. By this time she was so far recovered that she was discharged home. (The total dose of steroids amounted to 60 mg. of prednisolone and 1,900 mg. of hydrocortisone in 56 hours.) She did not develop serum sickness, and recommenced duty as a casualty officer on October 26 with strict instructions to avoid any contact with A.T.S. She has remained well. It was afterwards discovered that her father suffered from urticaria due to quinine, but no other family history of allergy was elicited. In view of the possibility that the reaction might have been due to the formation of immune A iso-antibodies (Crawford *et al.*, 1952), the patient's blood was examined. Her blood group was B, Rh positive. It contained ordinary anti-A but no alpha-haemolysins or incomplete anti-A.

Discussion

In view of the intense systemic reaction to the very small dose of tetanus antitoxin, there is little doubt that the initial urticarial swelling of the eyelids was a manifestation of allergy to horse serum. Whether the conjunctiva was the route by which she became sensitized it is impossible to prove; she had given injections of tetanus antitoxin some three years previously when a medical student, and it may have been at this time that she became sensitized. It is well known that the conjunctiva will show evidence of hypersensitivity, as at one time it was used as a site for a sensitivity test for tetanus antitoxin or other horse serum.

Though reactions to tetanus antitoxin are common, severe reactions are rare. Moynihan (1955) found some reaction after 5.29% of 7,580 injections; only two of these were so-called anaphylactic shock, and these were not severe.

The incidence of fatal reactions has been estimated at between 1 per 50,000 and 1 per 200,000 (Laurent and Parish, 1952). The reaction which did develop in the present case was in itself unusual, as there was no vasomotor collapse at the onset but a combination of rhinitis, asthma, and urticaria. Vomiting was a

prominent and distressing feature. The attack resembles closely that described by Baybutt (1959) in an infant who had received a first injection of gamma-globulin, but in that instance both parents had suffered from severe allergic disease.

Though the patient survived, the response to treatment was disappointing. Adrenaline, which was used perhaps in too small doses, had a very temporary effect on the asthma, and even large doses of antihistamine and steroids did not control the urticaria and vomiting for 48 hours.

My impression was that large doses of sodium phenobarbitone were more valuable than all the other measures, and, given the same situation again, I would use sedatives earlier.

Again in retrospect, the trial dose of tetanus antitoxin was too large, though it may be noted that the patient did not give a personal or family history of allergic disease. Parish, Laurent, and Moynihan (1957) suggest 0.2 ml. of a 1 in 10 dilution for subjects with a history of allergy, but a 1 in 100 dilution (with tenfold increments at intervals of half an hour) would be safer, though somewhat more tedious. The invalidism caused by serum sickness, the difficult decisions on whether to give tetanus antitoxin or not which face the casualty surgeon, and the occasional frightening reaction such as the present one, should give a stimulus to a bigger campaign of active immunization.

The considerable hazards of injecting tetanus antitoxin and the even greater risks of tetanus can both be eradicated by an all-out drive to increase active immunization. Personal records of all preventive inoculations—and of allergy, etc.—are very important.

Summary

A woman casualty officer developed urticarial swelling of the eyelids after giving tetanus antitoxin. Despite the absence of an allergic history, a test dose of 0.2 ml. of a 1 in 10 dilution of tetanus antitoxin precipitated a severe and prolonged allergic reaction. The asthma, urticaria, vomiting, and collapse lasted 48 hours, but subsided after adrenaline, antihistamines, and 1,900 mg. of hydrocortisone.

It is presumed that the patient was sensitized by tetanus antitoxin entering the conjunctival sacs. The intense reaction to a test dose of tetanus antitoxin confirmed the high degree of sensitivity which had developed. Such cases can be avoided only if a more vigorous active immunization campaign succeeds in making passive immunization unnecessary.

I wish to acknowledge the help given by Dr. Ivor Dunsford, of the Regional Blood Transfusion Centre, Sheffield, and the helpful comments and criticisms of Dr. H. J. Parish.

REFERENCES

Baybutt, J. A. (1959). *J. Amer. med. Ass.*, **171**, 415.
Crawford, H., Cutbush, M., Falconer, H., and Mollison, P. L. (1952). *Lancet*, **2**, 219.
Laurent, L. J. M., and Parish, H. J. (1952). *Brit. med. J.*, **1**, 1294.
Moynihan, N. H. (1955). *Lancet*, **2**, 264.
Parish, H. J. (1958). *Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment*, 4th ed. Livingstone, Edinburgh and London.
—— Laurent, L. J. M., and Moynihan, N. H. (1957). *Brit. med. J.*, **1**, 639.

Plans are being made to build a new leprosarium in the Karonga district of Nyasaland's Northern Province, where 33 people out of every 1,000 living on the lake shore are lepers.

EFFECT OF OXYGEN THERAPY ON OEDEMA IN PATIENTS WITH COR PULMONALE

BY

P. EFFERSÖE, M.D.
Resident Medical Officer

H. SUND KRISTENSEN, M.D.
Research Assistant

AND

H. C. A. LASSEN, M.D.
Professor of Epidemiology in the University of Copenhagen
Blegdam Hospital, Copenhagen

Peripheral oedema attending cardiac decompensation in patients with pulmonary insufficiency is often more resistant to ordinary treatment with digitalis, low-salt diet, and diuretics than oedema in primary heart disease.

The cases reported below are examples of how oxygen therapy, in some instances combined with artificial ventilation, may eliminate oedema in such patients under circumstances where other causes of the elimination can be left out of account.

Case 1

A man aged 40 submitted to thoracoplasty years ago for pulmonary tuberculosis. He was admitted to hospital on August 29, 1956, with diffuse pulmonary fibrosis, pronounced pulmonary insufficiency, and cor pulmonale, but with no signs of bronchitis or active tuberculosis. Before admission he had had increasing dyspnoea and moderate oedema, which had been treated with aminophylline, digitalis, oxygen, and mercaptomerin, with no effect.

On admission the patient was cyanotic and severely dyspnoeic. The liver was palpable one handbreadth below the curvature, and there was moderate oedema. The temperature was 37–37.6° C., B.P. 125/80, pulse rate 100–120/min.; weight 89.2 kg. Administration of digitalis was continued, and 1–2 litres of oxygen per minute were given through a nasopharyngeal catheter most of the time. On September 3 the patient was confused, and analysis of the arterial blood showed: oxygen saturation, 92%; pCO_2, about 120 mm. Hg; *p*H, 7.21. The patient was therefore placed in a tank respirator with an intratank pressure of −20/+7 cm. of water at a rate of 20 per minute, and 1 litre of oxygen per minute was admitted through the catheter. During the oxygen-and-tank treatment the arterial blood showed: oxygen saturation, 93%; pCO_2, 90-80 mm. Hg; *p*H, 7.28. The treatment was discontinued on September 6 owing to melaena. The urine volume trebled (Fig. 1) during the first 24 hours of oxygen-plus-tank treatment (September

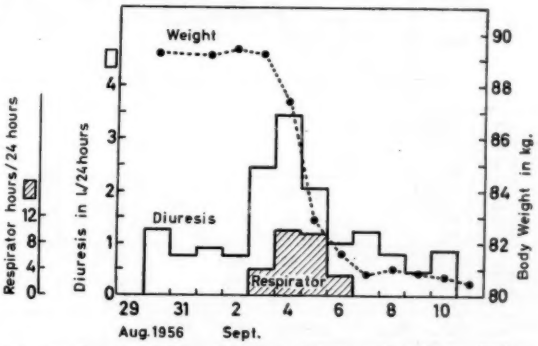


FIG. 1.—Case 1. Effect of oxygen therapy and tank ventilation on diuresis and body weight.

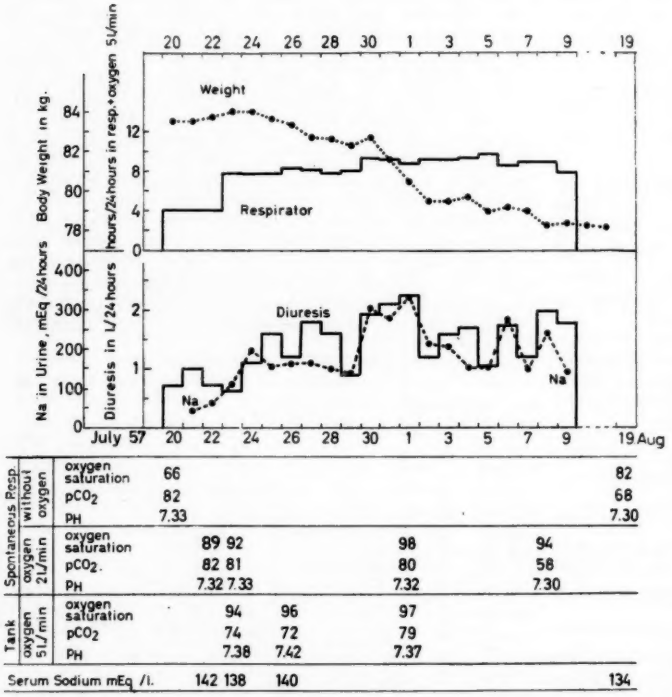
3). After four days the patient had lost 8 kg. and become free from oedema. During the period of treatment, as also during the weeks preceding this, he was given an ordinary mixed diet and a constant dose of digitalis, but no other therapy, more particularly no diuretics.

During repeated stays in hospital he several times obtained freedom from oedema in response to oxygen treatment in the tank respirator. A period of particularly thorough investigation is reported below.

The patient was readmitted on June 17, 1957, with extensive oedema but no signs of bronchitis. At home he had been given oxygen intermittently through nasal catheter, as well as mercaptomerin, digitalis, prednisone, and methylthiouracil, with no effect. In hospital, digitalis, prednisone, and methylthiouracil were administered in the previous dosages; and, in addition, the patient was submitted to moderate oxygen-and-respirator treatment. During the days before July 23 he received 2 l. of oxygen per minute through nasal catheter for an average of 14¼ hours a day, during four hours of which he was in a tank respirator. Despite this his weight increased, being 84 kg. on July 23. From this date the oxygen-plus-tank treatment was therefore intensified. The patient now received oxygen for an average of 15½ hours a day, of which 8–10 hours were spent in a tank respirator with 5 l. of oxygen per minute, and the rest of the time 2 l. per minute. The arterial oxygen saturation was 66% during spontaneous respiration without oxygen and 89–92% with oxygen, while in the tank respirator with 5 l. of oxygen per minute it was 94–97%. After intensification of the oxygen-plus-tank treatment the sodium excretion in the urine increased twofold or threefold, and the patient lost 6 kg., his weight being 78.3 kg. on August 8 (Fig. 2). During the first few days of oxygen-plus-tank treatment the pCO_2 fell to 72–74 mm. Hg.

The patient died a few months later of pneumonia. Necropsy revealed pronounced cor pulmonale, congestion of the liver, emphysema, oedema, and pulmonary infarcts.

Comment.—In an oedematous patient with chronic pulmonary insufficiency due to sequels of previous tuberculosis and thoracoplasty intense treatment with oxygen and tank respirator was three times immediately followed by elimination of the oedema. This could be attributed to no other therapeutic factors.



Spontaneous Resp. without oxygen	oxygen saturation	66				82
	pCO_2	82				68
	pH	7.33				7.30
oxygen 2l/min	oxygen saturation	89 92		98	94	
	pCO_2	82 81		80	58	
	pH	7.32 7.33		7.32	7.30	
Tank oxygen 5l/min	oxygen saturation	94	96	97		
	pCO_2	74	72	79		
	pH	7.38	7.42	7.37		
Serum Sodium mEq /l.		142 138	140			134

FIG. 2.—Case 1. Effect of oxygen therapy and tank ventilation on arterial blood values, diuresis, sodium excretion, and body weight.

Case 2

A woman aged 38, with pronounced kyphoscoliosis since childhood, was admitted to hospital on June 2, 1958, owing to increasing dyspnoea, with appreciable pulmonary insufficiency (Table I), pronounced jugular stasis, but

TABLE I.—*Arterial Blood Examinations in Case 2*

Date	Oxygen Therapy (l./min.)	Arterial Oxygen Saturation (%)	Arterial pCO_2 (mm.Hg)	Arterial *p*H
June 6 ..	0	63	42	7·44
,, 14 ..	0	67	62	7·36
,, 16 ..	2	72	46	7·43
,, 16 ..	4	92	62	7·34
,, 17 ..	4	94	74	7·32
,, 24 ..	4	86	84	7·30
,, 25 ..	0	60	56	7·46

without oedema, bronchitis, or pneumonia. B.P. normal; pulse rate about 100; temperature just over 38° C., but returning to normal during the first week. She was given oxygen intermittently the first four days, using a nasal catheter.

On account of increasing oedema she again received oxygen from June 12 to June 16, in doses of 2 l. per minute, this time 16½–18 hours a day. As her weight increased in spite of this, being 53 kg. on June 16 (Fig. 3), the oxygen treatment was intensified to 4 l. per minute. Three days later the patient excreted increased amounts of sodium and carbon dioxide with the urine (Fig. 3). The urine volume increased, and the weight dropped to 50 kg. Reduction of the oxygen treatment to 10–12 hours a day resulted in prompt redevelopment of oedema and a corresponding increase in weight. During the entire period she received a diet containing almost constant amounts of salt and fluid.

The patient died later, and necropsy revealed leathery pulmonary atelectasis in the lower lobes of both lungs. No pneumonia or infarcts were detectable.

Comment.—In a patient with chronic pulmonary insufficiency and increasing oedema the latter subsided after intense oxygen therapy, even though the pCO_2 increased and the *p*H fell during this treatment.

Case 3

A woman aged 52, with severe pulmonary insufficiency (see Table II) due to emphysema and pulmonary fibrosis, but no acute pulmonary disease, was transferred on December 10, 1958, from another hospital. The previous day she had received 300,000 units of penicillin twice and 500 mg. of chlorothiazide because of moderate oedema. The first two days her pulse rate was 100–120 with a few extrasystoles, and her temperature was slightly raised; but the temperature then returned to normal and the pulse rate fell to 80–90 without extrasystoles.

We continued with a low-salt diet and confinement to bed, but gave no other treatment—more particularly, no digitalis, oxygen, or diuretics. On December 16 the condition was thought to have become stationary, and oxygen treatment through a nasopharyngeal catheter was therefore started, at first with 1 l. per minute. The dose was increased gradually to 2.5 l. per minute.

On December 18 transitory auricular fibrillation occurred with 4:1 block, and on December 21 there were again transitory extrasystoles. The pulse rate remained unchanged.

The urine volume increased somewhat during the first few days of oxygen treatment, but a pronounced increase of the electrolyte excretion was first noticed after five to six days of treatment (Fig. 4). The oedema disappeared completely, and the patient lost 5 kg. (Fig. 4). She was later discharged in an improved state.

TABLE II.—*Blood Examinations in Case* 3

Date	Oxygen Therapy (l./min.)	Arterial Oxygen Saturation (%)	Arterial pCO_2 (mm.Hg)	Arterial *p*H	Serum Na (mEq/l.)
Dec. 16 ..	0	65	41	7·42	125
,, 17 ..	1	77	44	7·42	
,, 18 ..	1½	82	47	7·48	134
,, 19 ..	2	83	58	7·38	
,, 24 ..	2½	92	43	7·34	137
Jan. 7 ..	0	83	46	7·41	

Comments.—A patient with chronic pulmonary insufficiency and increasing oedema, which disappeared under intense oxygen therapy, even though the pCO_2 of the arterial blood increased and the *p*H fell.

In this patient, who had a low serum sodium concentration, the urine volume increased in the course of the first three days of treatment, whereas a rise of the electrolyte excretion was first noticed on the sixth day.

Discussion

Elimination of oedema during oxygen treatment of patients with cardiac oedema has been described (Barach and Richards, 1931; Richards and Barach, 1934). 12 out of 19 such patients developed increased diuresis during treament in an oxygen chamber with 40–50% oxygen. Among these 19 patients, one with cor pulmonale responded twice by elimination of oedema. The diuresis usually started after two to six days of treatment. The oxygen treatment was found to give not only an increased oxygen saturation of the arterial blood but also an increased carbon-dioxide content in the blood. The conditions presented by Cases 2 and 3 are in close accordance with these observations.

Possible Explanations of the Effect of Oxygen on Oedema

Oxygen treatment of patients with decompensated cor pulmonale tends to normalize the abnormally low oxygen tensions in (*a*) alveoli, (*b*) arterial blood, (*c*) tissue, and (*d*) venous blood. The response of the oedema to

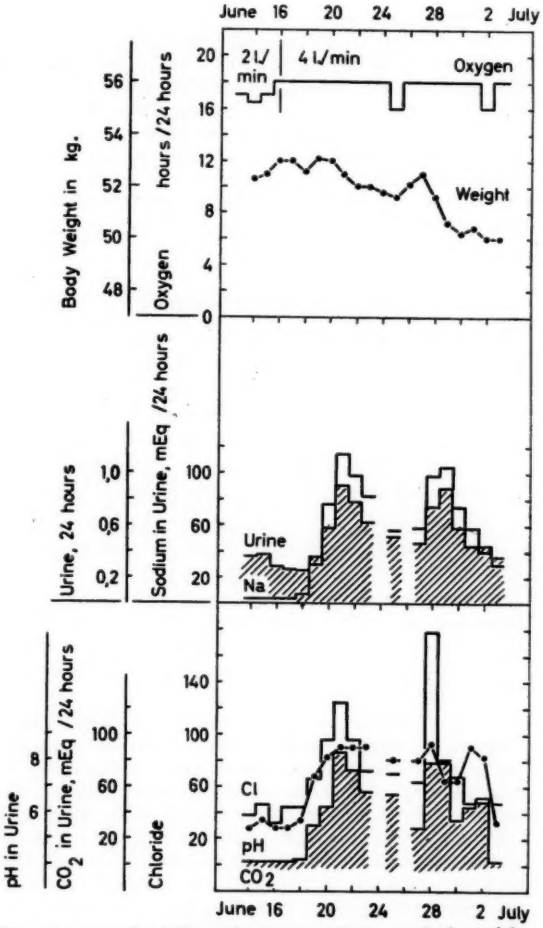


FIG. 3.—Case 2. Effect of oxygen therapy on body weight, diuresis, and urinary excretion of sodium, chloride, total CO_2, and urinary *p*H.

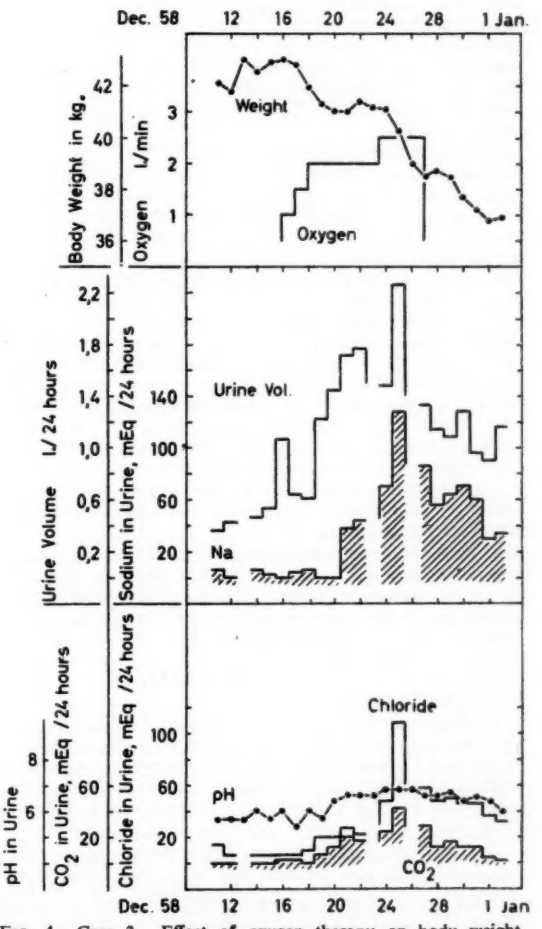


FIG. 4.—Case 3. Effect of oxygen therapy on body weight, diuresis, and urinary excretion of sodium, chloride, total CO_2, and urinary *p*H.

oxygen therapy must depend somehow or other on this tendency.

Oxygen Tension in Alveoli and Arterial Blood.—Patients with cardiac decompensation due to heart diseases other than cor pulmonale usually have normal or only slightly reduced alveolar and arterial oxygen tensions (Moltke and Worning, 1958). Accordingly, formation of oedema in these patients is not caused by a reduced oxygen tension in the alveoli and the arteries. If we take the mechanism of oedema formation to be the same in cor pulmonale as in other heart diseases, reduced alveolar and arterial oxygen tensions cannot be factors of decisive importance in the formation of oedema. Oxygen therapy is therefore rather unlikely to act via the oxygen tension in the alveoli and the arterial blood.

Oxygen Tension in the Tissues.—A reduced oxygen tension in the tissues is a feature that is common to all patients with cardiac oedema (Altschule, 1949). Tissue hypoxia may therefore be conceived to condition oedema formation in patients with cor pulmonale as well as in patients with other heart diseases. Oxygen may then be supposed to act by removing this condition. The question now arises how and from which tissues such an effect of oxygen therapy on the oedema is released.

1. The mechanism regulating respiration is greatly influenced by the oxygen tension. As we have seen elimination of oedema in association with both a rise (spontaneous respiration) and a fall (tank ventilation) of the carbon-dioxide tension and the hydrogen-ion concentration, the elimination is unlikely to be due to changes in pCO_2 and *p*H.

2. The blood circulation is likewise influenced by the oxygen tension. Case *et al.* (1955), in experiments on anaemic dogs, showed that a rise of the haemoglobin level in the coronary arteries causes the heart to perform the same work at a lower atrial pressure. If in our patients the myocardium was not optimally supplied with oxygen before the oxygen treatment, the latter might be accompanied by a fall of the pressure in the right atrium, even if the work of the myocardium remained unchanged. However, the work of the myocardium decreases when hypoxic patients with pulmonary insufficiency receive oxygen therapy, because this will reduce the raised pressure in the pulmonary artery, as well as the increased cardiac output, and the increased heart rate (Wilson *et al.*, 1955). If the capillary pressure varies parallel with the pressure in the right atrium, this might account for the elimination of oedema.

3. A better oxygen supply to the liver may normalize a decreased elimination of electrolyte- and fluid-retaining hormones (Chart *et al.*, 1956).

4. There is no evidence to suggest that a tendency towards normalization of the oxygen tension in the kidneys may cause elimination of oedema. On the contrary, Berger *et al.* (1949) found that hypoxia in normals was attended by an increased excretion of fluid and electrolytes; Fishman *et al.* (1951) observed—in short-period trials, it is true—that oxygen therapy to patients with hypoxia gave a reduced excretion of sodium.

5. Further, there is a possibility that receptors exist—for example, in the brain or the suprarenals—which are influenced by the oxygen tension, and which regulate the volume of the organism through the excretion of electrolytes and fluid by the kidneys—for example, on a hormonal basis.

Oxygen Tension in Venous Blood.—Oxygen tension receptors possibly exist in the central veins or in the pulmonary artery to regulate the fluid and electrolyte balance, as stated above, though such have never been demonstrated.

Does Treatment in Tank Respirator Effect Elimination of Oedema?

In Case 1 the oxygen saturation during the second period of oxygen-and-tank respirator treatment was only slightly higher than during spontaneous respiration with administration of oxygen. The question must therefore be considered whether the respirator treatment may alone have caused elimination of the oedema.

As stated above, the elimination of oedema is unlikely to be due to changes in carbon-dioxide tension and the hydrogen-ion concentration.

A probable explanation is that the respirator performs the rather straining work of respiration otherwise to be managed by the patient himself, thus improving the oxygen supply to the tissues.

The pressure variations to which our patient is exposed during artificial tank ventilation cause a higher mean pressure in the thorax compared with the rest of the body, a fact which has certain effects on the circulation: less filling of the thoracic portions of the vascular bed and a diminished cardiac output (Werkö, 1947; Motley *et al.*, 1948; Whittenberger and Sarnoff, 1950). This cannot explain the elimination of oedema, since Drury *et al.* (1947) have shown that an increase of the mean thoracic pressure is followed by a decrease of diuresis.

The number of respirations per minute was very nearly the same during treatment in the tank as while the patient was breathing spontaneously. Pressure variations in the thorax during the respiratory cycle were not measured. These would probably have been found to be greater in the tank than outside it. This might—via pressure-sensitive receptors in the thorax (Love *et al.*, 1957)—account for an increase of diuresis while the patient was in the tank respirator.

Conclusion and Summary

Oxygen therapy resulted in elimination of oedema in two patients with decompensated cor pulmonale.

In another patient with the same disease oxygen therapy and tank-respirator treatment was three times followed by elimination of oedema.

In all three patients the oedema was eliminated under conditions where other causes could probably be left out of account.

The possible explanation of these observations is discussed.

It is supposed that tissue hypoxia conditions the formation of cardiac oedema, and the oxygen therapy acts by removing this. We do not know how and from which tissues the oxygen tension exerts its influence on the fluid and electrolyte balance.

Respirator treatment alone may cause elimination of oedema. If so, this might be due to the respirator performing the work of respiration otherwise to be managed by the patient himself, thus reducing the oxygen consumption of the organism and consequently raising the oxygen tension of the tissues. Another possibility which must be taken into account is that increased pressure variations in the thorax during tank respiration might possibly influence the urinary output through the medium of pressure-sensitive receptors in the thorax.

REFERENCES

Altschule, M. D. (1949). *Physiology in Diseases of the Heart and Lungs*. Harvard Univ. Press, Cambridge, Mass.
Barach, A. L., and Richards, D. W., jun. (1931). *Arch. intern. Med.*, **48**, 325.
Berger, E. Y., Galdston, M., and Horwitz, S. A. (1949). *J. clin. Invest.*, **28**, 648.
Case, R. B., Berglund, E., and Sarnoff, S. J. (1955). *Amer. J. Med.*, **18**, 397.
Chart, J. J., Gordon, E. S., Helmer, P., and Le Sher, M. (1956). *J. clin. Invest.*, **35**, 254.
Drury, D. R., Henry, J. P., and Goodman, J. (1947). Ibid., **26**, 945.
Fishman, A. P., Maxwell, M. H., Crowder, C. H., and Morales, P. (1951). *Circulation*, **3**, 703.
Love, A. H. G., Roddie, R. A., Rosensweig, J., and Shanks, R. G. (1957). *Clin. Sci.*, **16**, 281.
Moltke, E., and Worning, H. (1958). *Acta med. scand.*, **160**, 397.
Motley, H. L., Cournand, A., Werkö, L., Dresdale, D. T., Himmelstein, A., and Richards, D. W., jun. (1948). *J. Amer. med. Ass.*, **137**, 370.
Richards, D. W., jun., and Barach, A. L. (1934). *Quart. J. Med.*, **27**, 437.
Werkö, L. (1947). *Acta med. scand.*, suppl. 193.
Whittenberger, J. L., and Sarnoff, S. J. (1950). *Med. Clin. N. Amer.*, **34**, 1335.
Wilson, R. H., Hoseth, W., and Dempsey, M. E. (1955). *Ann. intern. Med.*, **42**, 629.

POLYMYOSITIS

REPORT ON THREE CASES FROM WEST AFRICA

BY

B. G. BARNARD, M.R.C.P.

A. M. RANKIN, M.R.C.P., M.R.A.C.P., D.T.M.&H.

Senior Registrars, Department of Medicine, University College Hospital, Ibadan

AND

J. H. ROBERTSON, M.D.

Registrar, Department of Pathology, University College Hospital, Ibadan

The term "polymyositis" was first introduced by Wagner (1863) when he reported a case of acute generalized muscular affection with skin involvement which ended fatally within six days. Potain (1875) described a similar case in which the illness was less acute but which terminated fatally as a result of bronchopneumonia four to five months after the onset of the disease. Hepp (1887) gave a detailed account of the clinical features of a similar disorder, which he called pseudotrichinosis, and, while there were no skin lesions, the picture was that of a subacute polymyositis. Unverricht (1877) stressed the almost invariable occurrence of skin lesions in these cases, and therefore applied the name dermatomyositis to the condition. Subsequently he described the pattern of muscular involvement and pointed out that not all cases were fatal (Unverricht, 1891).

The first reported cases of this disease from Great Britain came from Gowers (1899) and Batten (1899), and though changes occurred in both skin and muscle in their patients they still used the term polymyositis to describe the condition. Oppenheim (1899, 1903) drew attention to the occasional involvement of mucous membrane and both ocular and cardiac muscle. He pointed out that the skin lesions could be sclerodermatous in character. Petges and Cléjat (1906) also stressed the extreme degree of atrophy and sclerosis of the skin (poikiloderma) that could occur, and described a chronic form of the disease.

It would appear from the above that much uncertainty has existed in the past about the relationship between dermatomyositis and other diseases of muscle without skin lesions, and only recently has it become established that dermatomyositis can occur without recognizable skin lesions. It is the purpose of this paper to describe three such cases, which represented clinically the acute, the subacute, and the chronic stages of the disease. All three cases occurred in Africans and are thought to be unique, as a review of the literature has shown that, apart from a single case in a Eurasian from South Africa (Sament and Klugman, 1957), the condition has so far not been reported in an African from this continent.

Case 1

A girl aged 16 was admitted to hospital with a five-days history of swelling and slight weakness of her arms and legs associated with pain on movement. The day after the onset of these symptoms she experienced some difficulty in swallowing, and this was followed the next day by the development of a nasal intonation to her voice.

At the time of examination her temperature was 100° F. (37.8° C.), and a striking clinical feature was swelling which involved particularly the arms and to a less extent the legs. The swelling in the upper limbs was confined to the forearms, while, in the lower limbs, the calves were mainly affected and the thighs only slightly so. The soft palate moved poorly but was otherwise normal, the gag reflex was elicited with difficulty, and water dripped from the patient's nose when drinking. A thorough and systematic examination of the central nervous system did not reveal the presence of any abnormalities, and the other systems were also normal.

In view of the findings on admission a tentative diagnosis of polymyositis was made, and this was later confirmed histologically.

Routine investigations were all normal, except Hb, 8.6 g./100 ml.

A biopsy specimen taken from the extensor muscles of the left forearm showed groups of muscle cells to be swollen, with intensely eosinophilic cytoplasm and a loss of their transverse striations and sarcolemma nuclei. The degeneration was patchy and was associated with a slight inflammatory infiltration composed mainly of lymphocytes and plasma cells.

As the patient was not acutely ill on admission, no specific therapy was given, pending the muscle-biopsy report. A week after admission, however, her temperature began to rise, the swelling of the arms increased, and the difficulty experienced in swallowing was greater. Assuming that the diagnosis was correct, prednisolone, 20 mg. eight-hourly, along with tetracycline, 250 mg. six-hourly, was given, the latter drug for controlling the bronchopneumonia which had developed. In addition, a Ryle tube was passed and intragastric feeding begun. In spite of these measures she steadily deteriorated, and finally died from extensive bronchopneumonia 16 days after admission.

Post-mortem Findings

The body was that of a well-nourished young female. The subcutaneous tissues of the arms and legs were the seat of a gelatinous oedema which was especially marked in the forearms. The underlying muscle was pale. Recent adhesions were present in both pleural cavities, and on the left side there was about half a pint (280 ml.) of straw-coloured effusion. Examination of the viscera showed extensive bronchopneumonic consolidation of the lower lobes of both lungs. The liver was the seat of a moderate degree of fatty infiltration and the spleen was enlarged, weighing 215 g. No other abnormal findings were observed macroscopically, and urine taken from the bladder showed no evidence of myoglobin on spectroscopic examination.

Sections were taken from the intercostal muscles, vastus lateralis, supinator of the forearm, diaphragm, soft palate, and oesophagus. While these varied in appearance, degeneration of the striated muscle fibres was prominent and affected small groups or even single fibres scattered unevenly throughout the sections. The cells were swollen and eosinophilic, they had lost their striations, and their sarcolemma nuclei were either shrunken or had disappeared. Elsewhere the fibres had become fragmented and were being phagocytosed by histiocytes. In other parts lesser degrees of damage were indicated by vacuolation and variation in the size of the muscle fibres. These changes were prominent in all the sections, except in those from the soft palate, where fibrosis was pronounced but where the remaining muscle appeared healthy. Inflammatory infiltration varied in degree in the muscles examined, and while virtually absent in the supinator muscle (Fig. 1) it was quite

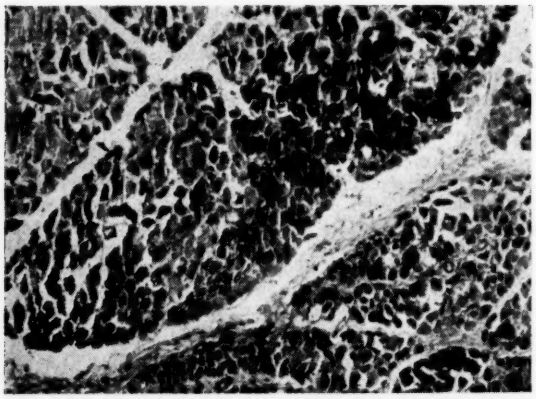


FIG. 1.—Case 1. Supinator muscle. Groups of swollen, deeply staining muscle fibres are present. There is no inflammatory reaction. (H. and E. ×96.)

pronounced in the striated muscle of the upper part of the oesophagus, the features here being very similar to those in Fig. 4. The inflammatory cells comprised plasma cells, lymphocytes, and histiocytes, with only occasional polymorphonuclear cells. In none of the sections did the small blood-vessels show any abnormalities.

Sections of the skin from forearm and thigh showed thickening of the dermis, both by oedema and by an increase of its collagen. A mild plasma-cell and lymphocytic infiltration was present and the hair follicles and sebaceous glands were atrophic. There was no evidence of fibrinoid degeneration of collagen, and the dermal vessels showed no abnormal features.

In the heart, the muscle bundles were separated by oedema fluid and there was a diffuse interstitial infiltration by mononuclear cells with some polymorphs. Changes in the cardiac muscle, however, were inconspicuous.

The liver showed periportal fatty infiltration, and deposits of malarial pigment were present in the spleen.

Case 2

A man aged 50, a Government official, was admitted to hospital for the investigation of symptoms of breathlessness with undue fatigue on exertion and loss of weight, these symptoms having begun three months earlier. In addition, he also complained of a slight cough which on occasion proved troublesome at night. His previous health had been good and his family and social history revealed nothing of relevance.

On examination he was pyrexial, with an increased respiratory rate, poor chest expansion, and bilateral basal crepitations in the lungs. No abnormal signs were found in any of the other systems. His blood-pressure was 120/70.

Routine investigations revealed nothing abnormal except (1) the E.C.G. showed some flattening of the T waves, and (2) chest *x*-ray examination showed bilateral basal bronchopneumonic changes.

Over the next few weeks he complained of increasing weakness and fatigue. His temperature varied from 98 to 100° F. (36.7 to 37.8° C.), rising on occasion to 101 to 102° F. (38.3 to 38.9° C.). Addison's disease was considered in view of an equivocal Kepler water-excretion test. However, treatment with cortisone, 12.5 mg. twice a day, produced no improvement.

One month after admission, when a firm diagnosis had still not been reached, the patient volunteered the information that he had been unable to raise his arms above his head while having his chest radiographed. In view of this a more thorough examination was made of the patient's musculo-skeletal system along with a further examination of the central nervous system; the following were the results.

There was an obvious degree of wasting and atrophy of the muscles of the shoulder-girdle which extended downwards to involve the proximal portions of the arms, these changes being more pronounced on the left side. The wasted muscles were weak, and in the upper limbs the movements most affected were abduction of the shoulder and extension of the forearm. In the lower limbs obvious wasting was not seen, but there was a marked diminution of power in the muscles of the pelvic girdle and thigh. In addition the muscles of the trunk were very weak, great difficulty being experienced by the patient in raising himself up in bed from the supine position. The neck muscles were also weak, the head tending to be held in the flexed position owing to the weakness of the extensors. Other muscles similarly affected were the intercostals, this resulting in respirations that were shallow and rapid and in the main diaphragmatic. Chest expansion was less than $\frac{1}{4}$ in. (2 cm.). No fasciculation was observed in any of the muscles, and neither myotonic nor myasthenic reactions were elicited. Muscle-swelling and tenderness were absent. The tendon jerks, though present, were diminished. Both plantars were flexor. Sensation, both superficial and deep, was intact throughout.

A few days later the patient noticed that if he drank fluids too quickly they trickled back through his nose. A re-examination of the cranial nerves at this stage showed that these were all normal and that both the soft palate and the pharynx showed no evidence of paralysis and appeared to move well. The cough reflex, on the other hand, though normal-sounding in character, was definitely diminished in intensity and ineffectual.

In view of the above and the finding of a urinary creatine excretion of 590 mg. in 24 hours, it was thought that he was

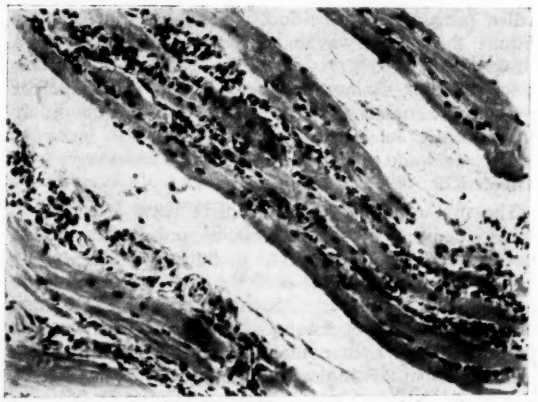


FIG. 2.—Case 2. Deltoid muscle. At the top left and extreme bottom right, degenerate muscle fibres are being invaded and phagocytosed by histiocytes. Also, towards the right, hyperplastic sarcolemma cells are arranged in short columns. (H. and E. ×111.)

probably suffering from a disease which involved muscle both primarily and extensively, and on these grounds a tentative diagnosis of polymyositis was made.

A biopsy specimen taken from the deltoid muscle showed the features of a subacute polymyositis (Fig. 2). There was a variation in size of the fibres, some of which were swollen and eosinophilic, with loss of their striations and sarcolemma nuclei. In several places it was seen that the change affected only a short segment of the fibre. Elsewhere necrotic fibres were being invaded by plasma cells and histiocytes, and undergoing phagocytosis and replacement by fibrous tissue. In some areas small basophilic fibres were prominent. These contained columns of large proliferated sarcolemma cells, the appearance being that which has been ascribed to muscle-cell regeneration.

Case 3

A woman aged 55 was admitted to hospital with a five-years history of increasing weakness of her arms and to a less degree of her legs, resulting in some difficulty in walking. She also complained of symptoms suggestive of a peptic ulcer. Her health prior to the onset of the original illness had been good. Her family history and obstetric history were also of no significance. She had had five pregnancies, all of which were normal, and the children were alive and well.

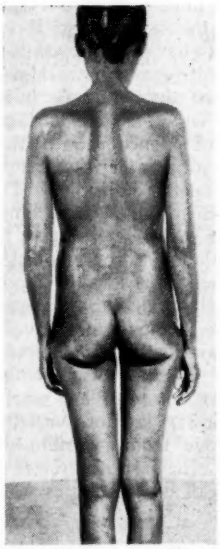


FIG. 3.—Case 3. Showing wasting of muscles of the shoulder-girdle.

On examination she presented as an elderly adult in whom the most striking clinical feature was a marked degree of wasting of the muscles of the shoulder-girdle (Fig. 3). The quadriceps femoris of both lower limbs was also atrophied. The atrophy was symmetrical in distribution, muscle tenderness was absent, and no fasciculation was observed in the muscles involved, or elsewhere. Power was greatly diminished in the deltoids and triceps on both sides, the patient being unable to abduct the shoulder or extend the elbow. It was also diminished, but to a less degree, in the biceps and the quadriceps femoris, these muscles appearing to be wasted rather than weak. A moderate degree of weakness in the trunk muscles was also noted. The tendon reflexes were absent in the arms and decreased in the legs. Both plantars were flexor and the abdominal reflexes were present. Sensation was intact throughout. Passive movements in all joints were painless and full in range.

Routine investigations revealed nothing abnormal. A barium-meal examination showed the presence of a large duodenal ulcer. The E.C.G. was normal. Lumbar puncture yielded normal fluid.

A biopsy specimen taken from the deltoid muscle (Fig. 4) showed degeneration of the muscle fibres with phagocytosis and replacement fibrosis. Extensive infiltration by plasma cells and lymphocytes was present, the appearances being similar to those seen in the oesophagus of Case 1. A skin biopsy of the V area of the chest showed no abnormal features.

Discussion

While it is now generally accepted that an acute type of polymyositis does occur, it is comparatively rare, and the disease more commonly presents in either a subacute or a chronic form. In the three cases described here, we were fortunate enough to see what we considered to be, on clinical grounds, all three types of the disease.

Case 1, though terminating fatally from an aspiration bronchopneumonia within three weeks of the onset of symptoms, offered little difficulty in diagnosis, for the patient presented with the characteristic features of the acute form of the disease—namely, fever, generalized muscle pain, and weakness with subcutaneous oedema. Dysphagia and regurgitation of fluids down the nose were also prominent symptoms, and sections taken from the oesophagus and the palate at necropsy showed both these structures to be involved in the disease process. No obvious skin lesions were seen at any stage of her illness, yet sections of the skin examined after death showed thickening of the dermis by oedema and an increase of its collagen content in addition to a mild round-cell and plasma-cell infiltration.

In retrospect it is felt that this patient's life might well have been prolonged, and perhaps a remission obtained, if a tracheotomy had been done soon after admission, as bronchopneumonia was undoubtedly the main cause of death in her case.

The clinical presentations of Cases 2 and 3 were in sharp contrast to that of Case 1, and they illustrate the wide range of clinical picture that may occur. It is in these subacute and chronic forms of the disease that difficulties in diagnosis may arise unless the protean nature of the symptomatology is recognized. Thus in the second patient exertional dyspnoea, cough, and basal crepitations in the lungs at first suggested a primary cardiac or respiratory disorder, though no evidence of cardiac enlargement was present radiologically. On recognition of the muscular weakness, however, it became clear that his symptoms were due to weakness of the respiratory muscles, resulting in an increase in respiratory rate and an accumulation of secretions in the lung bases, and also that his asthenia was similarly due to more generalized muscular involvement.

Case 3 presented with yet a different clinical picture, the salient features being chronic wasting and weakness of the proximal limb-girdle type, in which the arms were affected more severely than the legs. The diagnosis in this case was more difficult, and polyneuritis due to nutritional deficiency, which is common in Nigeria, as

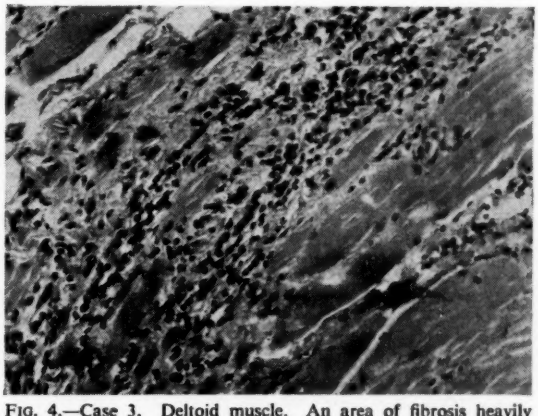


FIG. 4.—Case 3. Deltoid muscle. An area of fibrosis heavily infiltrated by plasma cells and lymphocytes is shown. Many of the remaining muscle fibres are degenerate. (H. and E. ×152.)

well as progressive muscular atrophy and degenerative lesions of the cervical spine, had to be considered.

Whereas the acute form of polymyositis presents with constitutional symptoms, muscle pain, and tenderness, these are all strikingly minimal or absent in the subacute and chronic forms of the disease (Eaton, 1954). Others have observed that, though striated muscle anywhere in the body could be involved, characteristically the proximal limb muscles and trunk muscles are chiefly affected (Biemond, 1948; Walton and Adams, 1958). It is this distribution of muscular wasting which has led to confusion with muscular dystrophy, so that muscle biopsy is essential for the diagnosis of most cases of subacute and chronic polymyositis. As the disease involves necrosis of muscle, creatinuria has been found to be a constant feature of it (O'Leary and Waisman, 1940; Jager and Grossman, 1944; Cumings, 1953), and persists as long as the disease remains active.

With regard to the prognosis of polymyositis and dermatomyositis, it is now well recognized that up to 50% of the florid cases terminate fatally, usually from pharyngeal or respiratory paralysis or from associated bronchopneumonia. In many of the others the disease becomes arrested, with varying amounts of residual disability (Oppenheim, 1903; Brock, 1934; O'Leary and Waisman, 1940; Sheard, 1951).

In conclusion, it is felt that rare and fatal conditions which have previously been reported from European communities in the temperate zones can also occur in tropical countries among the indigenous population, and that more and more of these conditions will doubtless be discovered as medical services, with adequate laboratory facilities to establish accurate diagnosis, become more readily available.

Summary

Three cases of polymyositis occurring in West Africans are described and the pleomorphic character of the clinical picture is discussed.

The literature is reviewed. Constitutional symptoms, it is generally agreed, are absent in the subacute and chronic forms of polymyositis and the presence of skin lesions is variable. Spontaneous remissions often occur.

The existence of the disease in West Africa is shown.

References

Batten, F. E. (1899). In *Allbutt's System of Medicine*, **7**, 461. Macmillan, London.
Brock, W. G. (1934). *Arch. Derm. Syph. (Chicago)*, **30**, 227.
Biemond, A. (1948). *Ned. T. Geneesk.*, **92**, 3486.
Cumings, J. N. (1953). *Brain*, **76**, 299.
Eaton, L. M. (1954). *Neurology (Minneap.)*, **4**, 245.
Gowers, W. R. (1899). *Brit. med. J.*, **1**, 65.
Hepp, P. (1887). *Berl. klin. Wschr.*, **24**, 389.
Jager, B. V., and Grossman, L. A. (1944). *Arch. intern. Med.*, **73**, 271.
O'Leary, P. A., and Waisman, M. (1940). *Arch. Derm. Syph. (Chicago)*, **41**, 1001.
Oppenheim, H. (1899). *Berl. klin. Wschr.*, **36**, 805.
—— (1903). Ibid., **40**, 381.
Petges, G., and Cléjat, C. (1906). *Arch. derm.-syph. (Paris)*, **7**, 553.
Potain (1875). *Bull. Soc. méd. Hôp. Paris*, **12**, 314.
Sament, S., and Klugman, L. H. (1957). *S. Afr. med. J.*, **31**, 430.
Sheard, C. (1951). *A.M.A. Arch. intern. Med.*, **88**, 640.
Unverricht, H. (1887). *Z. klin. Med.*, **12**, 533.
—— (1891). *Dtsch. med. Wschr.*, **17**, 41.
Wagner, E. (1863). *Arch. Heilk.*, **4**, 282.
Walton, J. N., and Adams, R. D. (1958). *Polymyositis*, p. 6. Livingstone, Edinburgh.

A CASE OF PROGRESSIVE HEMIATROPHY PRESENTING WITH SPONTANEOUS FRACTURES OF THE LOWER JAW

BY

PAUL BRAMLEY, M.B., B.D.S., F.D.S. R.C.S.Eng.

AND

ALEC. FORBES, D.M., M.R.C.P.

From the South Devon and East Cornwall Hospital, Plymouth

Hemiatrophy of the body is a rare recessive hereditary degeneration, which can affect the skin, connective tissue, muscle, bone, and peripheral nerves, and involve many organs and systems. It presents to specialists of widely separated interests, so that none may have a true picture of the disorder. To the neurologist it is progressive facial hemiatrophy, its usual textbook designation, and a rare cause of trigeminal neuralgia, epilepsy, and hemiplegia. To the dermatologist it is morphoea, scleroderma en coup de sabre, and various minor paracentral abnormalities of pigmentation of the hair and skin. To the dental surgeon it is a cause of unilateral malocclusion and dental deformity. To otolaryngology it contributes unilateral deafness and malformation of the sinuses. For gastro-enterologists it may induce dysphagia from unilateral atrophy of the oesophagus. It has also caused hypertension from unilateral kidney disease and unilateral diaphragmatic paralysis. To those interested in medicine as a whole its widespread modes of presentation will be of interest. To these is added another, of interest to surgeons, particularly those specializing in facio-maxillary work. Spontaneous fractures of the lower jaw are usually caused by weakening of the bone from infection or neoplasia. The following case is believed to be the first recorded one where the cause of the fractures was progressive facial hemiatrophy.

Case History

The patient is a widow aged 53, with one son. There has been no left-handedness, tic douloureux, or anything else of note in the family history. There were 11 siblings, three of whom have died of unknown causes.

At the age of 13 she had skin changes which began below the right breast and which slowly spread. Since this time the right arm and breast have always been smaller than the left.

At 33 exophthalmic goitre and pre-eclamptic toxaemia occurred, from which she recovered with termination of the pregnancy. She has had no injury, miscarriages, or blood transfusions. At 43 about four attacks of unconsciousness occurred without warning, in which she fell to the ground. She has bruised herself, but not been incontinent or bitten her tongue in these attacks. There was no observer. About this time Raynaud's phenomenon began, and persisted for some years, but she does not get this now.

At the age of 49, frontal and vertical headaches began, yielding to aspirin and usually associated with nausea and vomiting. These occurred several times a week, usually on waking. They have been less severe and without nausea for about a year. A few months after the headaches began, momentary jabs of severe pain in the right infra-auricular region developed. These radiated up into the temporal scalp

and would occur 50 to 60 times a day, every day. They lasted two months. About the same time similar pain lasting two to three seconds began in the right cheek and occurred 6 to 150 times a day. Talking and drinking brought on the pain, but there were no trigger points, associated salivation, lacrimation, or swelling of the face, though it occasionally flushed. Shortly after this she had a similar pain in the right lower jaw and would get spasms in which the jaw clenched on the right spontaneously, sometimes with the pain and sometimes not. At other times she would clench the jaw voluntarily with the pain, which was severe and not relieved by aspirin.

On October 12, 1953, after one bad spasm, the pain persisted and her face swelled. A spontaneous fracture of the neck of the right condyle of the mandible was found; it was treated by intermaxillary fixation and healed well. Both jaws were edentulous. She cannot remember whether a spontaneous contracture without pain initiated this fracture. No facial asymmetry was then observed. About this time numbness of the right lower lip and chin began, and has persisted. Koilonychia of the third and fourth fingers of the right hand developed an unknown time ago.

On June 12, 1957, while resting in a deck-chair, she had a severe muscular spasm and the right angle of her mandible was found to be fractured. A biopsy of bone taken from the fracture site was normal. The fracture was treated as before and united satisfactorily. On both occasions that the mandible fractured she was wearing full upper and lower dentures.

She was quiet and a good witness; she looked older than her age and had white hair. The right eye was indrawn and the right side of the face was smaller than the left in the upper part (Fig. 1). The muscles of the right arm, shoulder-girdle, and hand were all wasted (Fig. 2), but the muscular power was fair. All the tendon and cutaneous reflexes were present and equal and the plantar responses flexor. There was no evidence of spasticity on either side. There was an inconstant fasciculation of the muscles over the right side of the chin near the midline.

There were patchy sclerodermatous changes (morphoea) in the upper half of the body, all over the right shoulder, the arm, and forearm, where the skin was particularly thick and hard. A patch extended around the left side of the body, at the level of T 9. On the right temple, just in front of and above the ear, there was an oval patch without hair, slightly violaceous in the centre, in which the skin was thickened and atrophied. The legs were unaffected and equal in size. The right breast was smaller than the left. The remainder of the physical examination, including the fundi, showed nothing abnormal. Her blood-pressure varied between 100/80 and 175/95. The urine contained no albumin or sugar. *X*-ray examination showed: skull and mandibles, no abnormality; humeri, no lesion, equal in size; hands, several phalanges showed an abnormal increase in density on the right side; cervical spine, generalized spondylosis C 4 to 6, abundant calcifications seen in the thyroid. I.V.P. was normal. Barium swallow showed no abnormality of oesophagus. Haemoglobin, 91%; W.B.C. 7,000; E.S.R. 7 mm. per hour (Westergren); normal differential and film appearances. Plasma cholesterol 297 mg./100 ml. W.R. and Kahn, negative. Serum alkaline phosphatase 5.5 and 2.9 K.-A. units per ml. Serum calcium, 8.4 mg./100 ml. Serum inorganic phosphate, 3.4 mg./100 ml. E.E.G. (Dr. N. S. Alcock): "The resting record is normal. In one of her spasms only muscle activity was seen. There is a flat channel over the scarred area on the right side. There is no evidence of neurogenic activity as a basis for her spasms."

Myography (Squadron-Leader J. L. Milligan).—"I performed intensity duration curves on three muscles on each side—abductor digiti minimi, triceps, and tibialis anterior. The curves for the right side were all normal, but the curves for the left side showed a more sluggish response and a kinked curve most noticeable in the abductor digiti minimi. This could indicate a partial denervation. Electromyography was performed on all the above muscles. In only one muscle, left triceps, was there any evidence of spontaneous activity, and this I do not think was truly spontaneous, as it could be eliminated by contracting the antagonist. There was no evidence of fibrillation to support the intensity duration curve. On volition, the left side showed normal recruitment of motor units, the amplitude and duration of which were normal. The interference pattern was complete. On the right side, on volition, the motor units were much larger in amplitude, some being as large as 8 millivolts and 10–15 milliseconds in duration. A full interference pattern was produced on maximal volition, but of a much higher amplitude than on the left side. There was no evidence of an increased number of polyphasic potentials as compared with normal. The picture over all, then, is normal on the left except for some small deviation in intensity duration curves, which could stand being repeated at a later date. On the right side, the large motor unit responses may mean that there is a lesion in the cord affecting the small motor unit cells as in poliomyelitis, but one would then expect to find an abnormal intensity duration curve and the presence of fibrillation."

Local anaesthesia of the mental nerve relieved the spasms of pain, and peripheral neurectomy was performed. This gave relief for only a week. Infraorbital nerve blocks gave no relief.

She was therefore referred to Mr. G. Alexander for consideration of section of the Gasserian sensory roots. Temporary block of this ganglion relieved her pain, and on March 20, 1958, Mr. Alexander avulsed slightly more than the outer half of the root from the posterior limb of the ganglion. The motor root was preserved. This resulted in analgesia of the face to the level of the lower eyelid and retention of corneal reflex. The patient's constant pain was abolished and also the trigeminal neuralgia.

FIG. 1

FIG. 2

Subsequently she remained well, but still had painless attacks in which the muscles of the right side of the face bunched up. These have not been observed.

In June, 1958, pain developed in the back of the neck. Grating of the cervical spine was noted, and *x*-ray films showed spondylosis. Traction of the neck in hospital has not relieved this pain. In December, 1958, she reported intermittent sweats all over the body and a slight increase of the weakness of the right side, but there

was no objective change. She remained pleased to have had the partial Gasserian neurectomy.

Discussion

Hemiatrophy of the body is usually facial, and not always progressive and unilateral. Like other hereditary degenerations, most cases begin near adolescence. Wartenberg (1945) reviewed the subject thoroughly. The present case has the typical features of onset at puberty, scleroderma, fits, trigeminal neuralgia, muscular spasms, sweats, and slow progression.

There is no evidence of involvement of the internal organs in the hemiatrophy. The E.E.G. showed no evidence of epilepsy. The findings on myography are not clear. Possibly there may be a cord lesion on the right, and there is no evidence of an upper motor neurone lesion affecting the muscles of the left side. Cases in which this occurs have been described by Brain (1955), Reider and Player (1946), and Wartenberg (1945), who quoted several other instances. The operative results suggest that the cause of the trigeminal neuralgia was peripheral.

The segment of scleroderma on the opposite side of the body suggests that in this case the factor controlling the process is not confined to the right. It is assumed that the scleroderma and the hemiatrophy have a common origin on the evidence collected by Wartenberg (1945). Urechia and Retezeanu (1936) have reported a case of right hemi-facial atrophy with atrophy of the opposite arm, and Thoma (1954) mentions others in which the hemiatrophy was patchy and bilateral.

The spontaneous fractures of the jaw, with which this case presented, are believed not to have been described before in a case of hemiatrophy of the body. The cause was probably intense spasm of the right side of the face due to the trigeminal neuralgia, often found in this condition, acting on a jaw weakened by the hemiatrophy.

Summary

A case of progressive hemiatrophy is described, in which the patient twice suffered a spontaneous fracture of the edentulous mandible on the affected side, attributed to facial spasm associated with trigeminal neuralgia.

BIBLIOGRAPHY

Brain, Sir R. (1955). *Diseases of the Nervous System*, 5th ed. Oxford Univ. Press, London.
Reider, N., and Player, G. S. (1946). *J. nerv. ment. Dis.*, **103**, 1.
Thoma, K. H. (1954). *Oral Pathology*, 4th ed. Mosby, St. Louis.
Urechia, C. I., and Retezeanu (1936). *Bull. Soc. méd. Hôp. Paris*, **52**, 398.
Wartenberg, R. (1945). *Arch. Neurol. Psychiat. (Chicago)*, **54**, 75.

Since the discovery of the curative powers of the sulphones, interest in leprosy has increased, campaigns have been launched bringing as many as possible of the estimated 10 to 12 million people affected throughout the world under treatment, and more doctors are engaged in research into the unsolved problems of the disease. W.H.O. has played a leading part in spreading knowledge of advances in treatment and in helping organize leprosy campaigns in countries where the disease is an important public-health problem, and its work is described in the booklet *International Work in Leprosy, 1948–59*, and is set against the background of a short history of leprosy, its incidence, its treatment, and the research and other problems it raises. (Available from H.M.S.O., P.O. Box 569, London, S.E.1.)

THE INHERITANCE OF ESSENTIAL PENTOSURIA

BY

P. D. ROBERTS, M.D., D.Path.
Senior Registrar to the Clinical Laboratories, the London Hospital

Essential pentosuria is a rare condition characterized by the constant excretion of xyloketose in the urine. Included by Garrod (1923) among the inborn errors of metabolism, the condition probably results from a block in the metabolism of xyloketose, one of the normal products of glucuronic acid metabolism (Enklewitz and Lasker, 1935; Flynn, 1955).

This report describes the finding of xyloketosuria in a mother and her two children.

Methods.—The following methods were used to investigate the reducing substance in the urine: (1) qualitative Benedict's test for urine reducing substance; (2) Bial's test for pentoses; (3) the Lasker–Enklewitz test for xyloketose (Lasker and Enklewitz, 1933); (4) osazone preparation; (5) paper chromatography (Horrocks and Manning 1949) using 3:2:1.5 *n*-butanol-pyridine-water solvent (Hough *et al.*, 1950), demonstrating the sugar spots with aniline hydrogen oxalate; (6) quantitative estimation of the urine xyloketose (Lasker and Enklewitz, 1933), using the factor of Greenwald (1930) for the calculation.

Cases

The propositus, a Jewish woman aged 40 (E.R.), was admitted to the National Hospital, Queen Square, complaining of unsteadiness of gait, giddiness, and nausea for two years. The symptoms dated from a hysterectomy for fibroids two years previously, and no organic cause for them was found. During investigation this patient was found to have a reducing substance in the urine; it transpired that this had been first noticed in 1939 and on a number of occasions since, resulting in three normal glucose-tolerance curves and the warning that she was "knocking on the door of diabetes."

On the present admission the urine showed a constant yellowish-green precipitate with Benedict's solution; a glucose-tolerance curve was normal (fasting blood-sugar 98 mg./100 ml.; half-hour, 155 mg.; 1 hour, 138 mg.; 1½ hours, 115 mg.; 2 hours, 112 mg.; 3 hours, 80 mg.), with no alteration of the amount of reducing substance in the urine during the test. The urine gave a positive Bial test for pentose and a positive Lasker–Enklewitz test for xyloketose. An osazone was prepared, showing fine needles similar to glucosazone, but smaller. Glucose-oxidase test paper ("clinistix"), specific for glucose, was negative. Paper chromatography with suitable markers showed a pentose

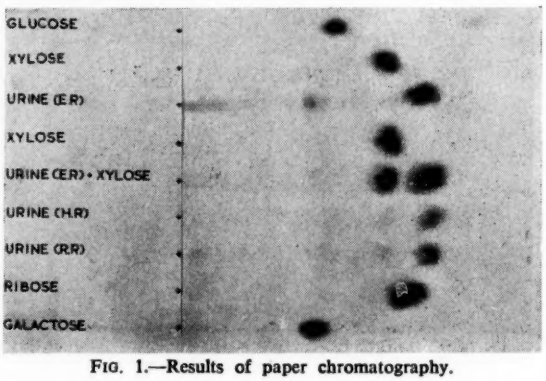


FIG. 1.—Results of paper chromatography.

in the xyloketose position (Fig. 1). Quantitative estimation showed 0.55 g./100 ml. of this reducing substance in the urine.

Family Investigation.—Investigation of the immediate family revealed xyloketosuria in the patient's two children, a boy aged 12 (H.R.) and a girl aged 9 (R.R.), the methods of testing being those used with the mother. Chromatography of the three positive urines is shown in Fig. 1. Quantitative estimation showed 0.30 g./100 ml. in the boy's urine and 0.13 g./100 ml. in the girl's urine. An extensive survey of the family (Fig. 2), using Benedict's test and the Lasker–Enklewitz test for screening, revealed no further positive cases.

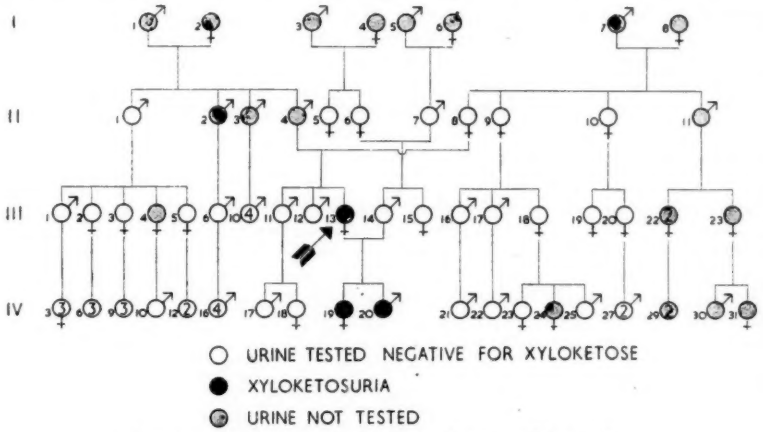


FIG. 2.—Genealogical tree of family showing xyloketosuria.

Discussion

Since the first description of xyloketosuria by Salkowski and Jastrowitz (1892), some 200 cases have been reported. In this country Cammidge and Howard (1920) recorded seven cases, but the exact diagnosis in these is uncertain; Flynn (1955) reported two unrelated cases proved by chromatography. Xyloketosuria is an apparently entirely benign condition, with a normal expectation of life (Lasker, 1955).

In the most comprehensive study of xyloketosuria, Lasker *et al.* (1936) reviewed the published cases and reported their own series of 37 individual cases in 20 families. They concluded from their survey that the condition was inherited and probably controlled by a simple recessive gene. They noted that xyloketosuria was very rare in the general population but often found in the families of known cases. Blatherwick (personal communication to Lasker *et al.*, 1936) found an incidence of 1 in 50,000 from Metropolitan Life Insurance records, but admitted that a number of cases excreting less than 0.25% of xyloketose may have been missed. On the other hand, Lasker *et al.* (1936) found 10 new cases on testing 34 sibs of xyloketosuric propositi; in one family 66 individuals were tested and seven cases found. The condition is almost, if not entirely, confined to Jews, though Barnes and Bloomberg (1953) described the condition in an apparently non-Jewish family.

In the series of Lasker *et al.* (1936) xyloketosuria was found in the children of 10 families in which neither parent was positive. In these 10 sibships 16 out of 38 members had xyloketosuria: deducting the eight propositi, there remained 8 out of 30 members. This series included one case, the child of first cousins, one parent being affected.

The recessive inheritance of the condition has been generally accepted by other writers, though Schultsz (1938) described four cases in two generations—a father and his two sons, and a brother—and concluded that the condition was inherited as a dominant characteristic. Macumber (1949) found xyloketosuria in a father and two sons.

The findings in the present family are consistent with the recessive hypothesis, provided one assumes that the mating of Case III 13 with Case III 14 (Fig. 2) is between a xyloketosuric who is homozygous with a heterozygote. Both these individuals are Jewish, the parents of Case III 13 (E.R.) coming from a small town near Warsaw and those of Case III 14 from Odessa and Leningrad. Lasker (personal communication) believes that the incidence of xyloketosuria among Jewish people originating from Central and Eastern Europe may be as high as 1 in 1,500. This means that the frequency of heterozygotes must be of the order of 5% of the population and the chance of a xyloketosuric marrying an unrelated heterozygote would not be remote. An attempt was made by comparing family names to establish a connexion between the present family and some of Lasker's cases originating in Warsaw and Odessa, but no such connexion could be traced.

It is unfortunate that, with the increasing use of glucose-specific enzyme test papers for urine-testing in place of Benedict's or Fehling's tests, these interesting cases will not be recognized. With this type of glucose-specific test other reducing substances in the urine will also be missed, some of which—for example, galactose—are of direct clinical importance.

Summary

The unusual occurrence of xyloketosuria is reported in a mother and her two children. The family had originated from known pockets of high incidence for xyloketosuria in Poland and Russia. An extensive survey of the family showed no further cases.

I am grateful to Dr. Macdonald Critchley for permission to investigate a case under his care and to Professor J. N. Cumings for his advice and encouragement. I thank Dr. Margaret Lasker for most interesting information on her investigations of this condition.

REFERENCES

Barnes, H. D., and Bloomberg, B. M. (1953). *S. Afr. J. med. Sci.*, **18**, 93.
Cammidge, P. J., and Howard, H. A. H. (1920). *Brit. med. J.*, **2**, 777.
Enklewitz, M., and Lasker, M. (1935). *J. biol. Chem.*, **110**, 443.
Flynn, F. V. (1955). *Brit. med. J.*, **1**, 391.
Garrod, A. E. (1923). *Inborn Errors of Metabolism*, 2nd ed. Frowde, London.
Greenwald, I. (1930). *J. biol. Chem.*, **88**, 1.
Horrocks, R. H., and Manning, G. B. (1949). *Lancet*, **1**, 1042.
Hough, L., Jones, J. K. N., and Wadman, W. H. (1950). *J. chem. Soc.*, p. 1,702.
Lasker, M. (1955). *Hum. Biol.*, **27**, 294.
—— and Enklewitz, M. (1933). *J. biol. Chem.*, **101**, 289.
—— —— and Lasker, G. W. (1936). *Hum. Biol.*, **8**, 243.
Macumber, H. H. (1949). *J. Okla. St. med. Ass.*, **42**, 281.
Salkowski, E., and Jastrowitz, M. (1892). *Zbl. med. Wiss.*, **30**, 337.
Schultsz, J. C. (1938). *Onderzoekingen over Pentosurie*. Kosmos, Amsterdam.

EFFECT OF MALARIA CONTROL ON HAEMOGLOBIN LEVELS

BY

C. C. DRAPER, B.M., B.Ch., D.P.H., D.T.M.&H.
East African Institute of Malaria

From 1954 to 1959 an experiment was in progress in the plains of the Taveta-Pare area of Kenya and Tanganyika, which are about 2,000 ft. (610 metres) above sea-level, to control rural hyperendemic malaria and to assess some of the effects of this, if successful, upon the health of the people. For the latter purpose several investigations were done, including the measurement of haemoglobin levels, and this paper describes the results of these.

After a year and a half for the collection of basic data, the first spraying of all native huts with the residual insecticide dieldrin was started in the latter part of 1955, the sixth and final spraying being completed in early 1959. Descriptions of the malaria before the spraying, and of the considerable reduction in transmission later effected, have been given by Smith and Draper (1959) for the Taveta area, and by Draper and Smith (1957, 1960) for the South Pare area. Serial measurements of haemoglobin, and other investigations, were done on a sample of about 2,000 people, of whom slightly less than one-third came from the Taveta area and the others from the South Pare area. The intention was to examine the same people on each occasion; and this was about 80% successful; of 100 people on the registers, about 80 would appear for examination at one survey. Infant clinics were run in the Pare area to study several aspects of infant health, and the results of haemoglobin estimations from these have been included here.

Table I shows the spleen and parasite rates, before and after three years of spraying, of those groups in Taveta and Pare on whom the haemoglobin estimations were done, and demonstrates the great reductions in the malaria indices by 1959. Before the spraying, malaria was hyperendemic, with heavy infection in infancy and childhood, but with evidence of the later development of some immunity to infection. This was typically manifested by a fall with increasing age in the density of infections, the highest densities occurring at the ages of 2 or 3 years. Over 90% of infections were of *Plasmodium falciparum*. At a preliminary medical survey in the Pare area, infections with *Schistosoma haematobium* and with hookworm were found to be common, and in the Taveta area infection with *S. mansoni* was common. There is no reason to think that there has been any change in the incidence of these infections during the period of these observations. There has, however, particularly in the Pare area, been a noticeable rise in the general economic level since 1955.

TABLE I.—*Spleen and Parasite Rates, Before and After Three Years' Residual Spraying, of People on Whom Haemoglobin Estimations were Done*

Age-groups	No. Examined	Spleen Rate %		Parasite Rate %	
		Feb.–June, 1955	Sept., 1958–Feb., 1959	Feb.–June, 1955	Sept., 1958–Feb., 1959
0–11 months	44– 62	50	10	61	0
12–23 ,,	41– 77	78	1	84	2
2– 4 years	122–126	88	2	86	5
10–14 ,,	240–320	77	14	73	7
10–14 ,,	245–299	68	16	62	4
15–19 ,,	115–141	46	11	49	4
20–39 ,,	157–458	55	22	29	4
40+ ,,	134–379	56	31	33	3

In addition, haemoglobin surveys were done in a school in the malaria-free Pare mountains, at an altitude of 4,000 ft. (1,220 metres), and in a lowland comparison area some 70 miles (112 km.) south of the sprayed zone, where malaria remained uncontrolled.

Estimations of haemoglobin were made with the M.R.C. photometer. Samples of blood were collected in the field in the mornings, and the estimations were done in the laboratory during the afternoons. The great majority of the estimations were done by me. Some total white-cell counts were done by the method given by Dacie (1950).

Results

Table II and the Chart show the mean haemoglobin levels in the Taveta-Pare areas at two surveys before the spraying and at three later surveys. Infants under 3 months old have been omitted because of the rapid physiological variations in haemoglobin during the first few months of life. Before the spraying, all groups showed some degree of anaemia, this being most pronounced in the infants and young children and in the adolescent and adult females. After the start of malaria control there has been a progressive rise each year in the mean levels; the figures for all groups at the last survey are significantly greater than those at the first survey, the differences between the means being from 3 to 10 times the standard errors of their differences. Table III shows, for each group, the percentage increases in the means from the first to the last surveys. The greatest proportional increases have been in the infants and young children, and the least in the girls and young

TABLE II.—*Mean Haemoglobin (g./100 ml.) at 5 Successive Surveys*

Sex and Age	Feb.–June, '55			Aug.–Nov., '55			Feb.–June, '57			Feb.–June, '58			Aug., '58–Feb., '59		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Both Sexes:															
3–11 months	40	9·2	1·6	112	9·4	1·7	131	10·9	1·4	176	10·7	1·3	106	10·9	1·2
12–23 ,,	40	8·9	1·8	68	9·4	2·1	73	10·9	1·6	84	10·8	1·3	87	11·2	1·1
2–4 years	108	10·4	1·5	68	10·2	1·7	105	11·5	1·5	119	11·6	1·3	102	12·2	1·4
5–9 ,, ..	245	11·6	1·5	110	11·2	1·4	254	12·4	1·6	296	12·5	1·4	250	12·9	1·1
Males:															
10–14 years	156	12·0	1·5	48	11·5	1·6	130	12·9	1·4	123	12·9	1·4	132	13·1	1·2
15–19 ,,	44	12·9	1·5	27	13·2	1·5	32	13·7	2·4	71	14·2	1·7	63	14·8	1·7
20–39 ,,	182	13·5	1·8	130	13·1	1·9	147	14·3	1·8	139	14·7	1·5	121	15·2	1·5
40+ ,,	163	12·6	1·9	107	12·6	1·9	153	13·6	1·8	196	13·9	1·9	133	14·5	1·5
Females:															
10–14 years	104	12·3	1·6	33	11·6	1·5	108	12·8	1·6	119	13·0	1·2	87	13·2	1·1
15–19 ,,	82	12·0	1·9	51	10·9	1·9	59	12·0	1·8	56	12·4	1·8	57	13·0	1·5
20–39 ,,	215	11·6	1·8	145	11·2	1·5	191	12·4	1·6	219	12·3	1·6	182	12·9	1·4
40+ ,,	130	11·6	1·6	86	10·9	1·8	134	12·2	1·7	159	12·5	1·8	92	13·4	1·4

No. = Number examined. S.D. = Standard deviation.

adult females. Pregnant females were 5 to 10% of the age-groups 15 to 19 years and 20 to 39 years, the higher proportion being at the later surveys, as another effect of malaria control was to increase the fertility rates. Their haemoglobin levels were generally lower than those of other females: 37 pregnant women examined at the first two surveys had a mean level of 10.0 ± 1.8 g., and 80 examined during the last three surveys had a mean level of 11.5 ± 1.2 g.

As analysis of some of the individual surveys suggested that there might be some relation between haemoglobin and splenomegaly, an analysis was done of the figures for the first and the last three surveys together, comparing the mean haemoglobin levels of those with and without palpable spleens. This is given in Table IV. There are differences in all groups, which are statistically significant except for the males aged 15 to 19 years and 40 and over.

Table V shows the haemoglobin levels, at several surveys, of children in the comparison area and in the Pare mountain school. The former show no changes over the period of observation. The latter initially had higher levels than the children in the Pare plains, perhaps in part due to the altitude, but they also show changes over three years. These, though statistically significant, are less than the changes in the plains, and may be due to general improvement in living conditions, this area being one of the most developed in the Pare district.

Despite the improvement in haemoglobin levels in the plains after malaria control, anaemia was still common, especially in children and young women. To see if this would respond to additional iron in the diet, a group of 23 schoolchildren, with a mean haemoglobin before treatment of 10.9 ± 0.7 g., were given 1 g. of ferrous sulphate daily for five days a week over a month. At the end of this period their mean haemoglobin had risen to 12.3 ± 1.6 g.

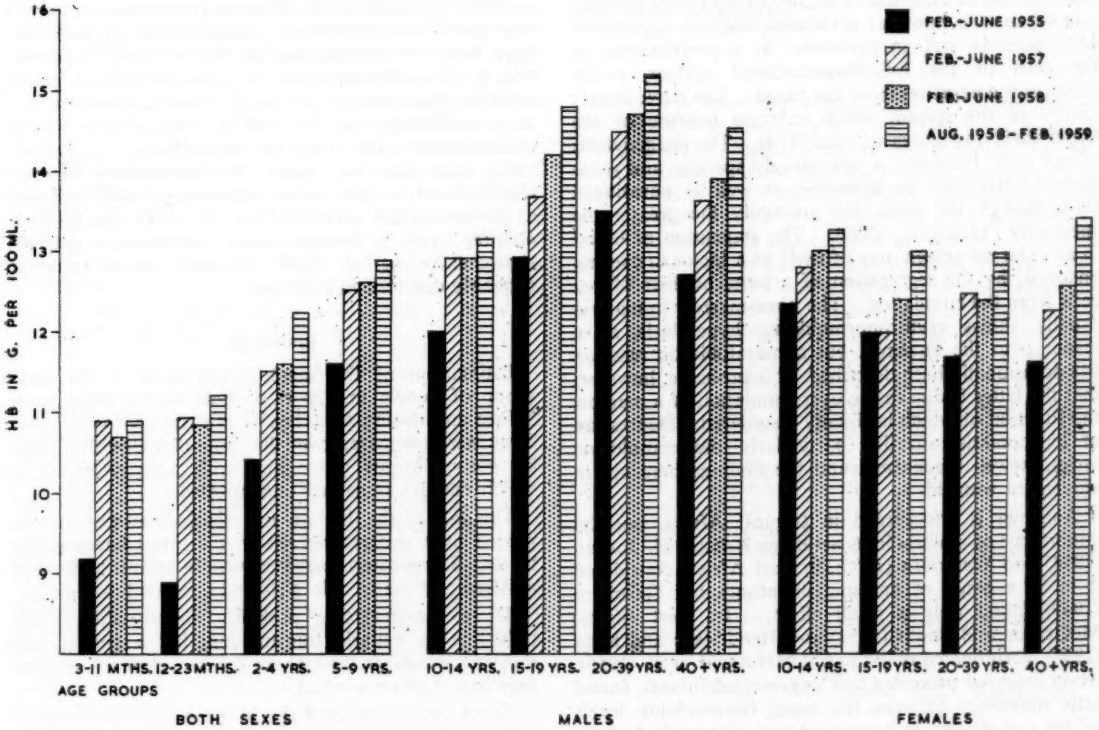
The results of two series of total white-blood-cell counts, before and after malaria control, are given in Table VI. All groups show an increase, but the changes are statistically significant only for the two younger age-groups.

TABLE III.—*Percentage Increases in Mean Haemoglobin Levels from First to Last Survey, by Age and Sex*

Age	Both Sexes (% Increase)	Age	Males (% Increase)	Females (% Increase)
3–11 months	18·5	10–14 years	9·2	7·3
12–23 ,,	25·8	15–19 ,,	14·7	8·3
2– 4 years	17·3	20–39 ,,	12·6	11·7
5– 9 ,,	11·2	40+ ,,	15·1	15·5

TABLE IV.—*Mean Haemoglobins (g./100 ml.) by Spleen Size*

Sex and Age	Spleen Palpable			Spleen Not Palpable		
	No.	Mean	S.D.	No.	Mean	S.D.
Both Sexes:						
3–11 months	11	9·2	1·7	160	10·8	1·5
12–23 ,, ..	11	8·4	1·4	155	11·0	1·3
2– 4 years ..	82	9·8	1·4	305	11·8	1·5
5– 9 ,, ..	279	11·8	1·7	599	12·8	1·4
Males:						
10–14 years ..	191	12·3	1·5	319	13·2	1·2
15–19 ,, ..	61	13·5	2·0	144	13·8	1·9
20–39 ,, ..	188	14·1	1·8	347	14·7	1·6
40+ ,, ..	245	13·5	1·8	357	13·7	1·8
Females:						
10–14 years ..	128	12·4	1·4	274	13·1	1·3
15–19 ,, ..	58	11·6	1·3	177	12·5	1·7
20–39 ,, ..	201	11·9	1·6	510	12·5	1·5
40+ ,, ..	173	11·9	1·8	321	12·6	1·6



Changes in mean haemoglobin levels, by age and sex, after malaria control.

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TABLE V.—*Mean Haemoglobins in Comparison Area and in Mountain School (g./100 ml.)*

Sex and Age	Kiloza Comparison Area									Usangi School					
	Mar. and June, '56			May, 1957			June, 1958			May, 1955			May, 1958		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Both Sexes:															
2–4 years	28	10·8	1·7	52	10·1	1·1	22	10·4	1·3	—			—		
5–9 ,,	99	11·9	1·4	91	11·8	1·3	97	11·5	1·1	79	12·7	1·0	101	13·3	1·1
Males:															
10–14 years	61	11·9	1·6	23	11·5	1·6	62	11·6	1·2	70	13·2	1·1	80	13·8	1·1
Females:															
10–14 years	46	12·2	1·6	30	12·7	1·2	48	11·9	1·2	43	13·3	1·1	48	13·8	1·0

TABLE VI.—*Mean Total White-cell Counts per c.mm.*

Age and Sex	1955			1958		
	No.	Mean	S.D.	No.	Mean	S.D.
Both Sexes:						
2–9 years ..	92	8,260	1,890	96	9,350	2,690
10–19 ,, ..	141	7,270	1,970	110	7,940	2,128
Males:						
Over 20 years	84	6,950	1,620	56	7,250	2,722
Females:						
Over 20 years	72	6,330	1,700	53	6,720	1,660

Discussion

The possible causes of anaemia in malaria are several. In the acute stage of infection there is intravascular haemolysis of parasitized cells at sporulation, and, of equal if not of greater importance, the lysis of normal cells, resulting from a disturbance of the normal balance of lytic systems in the blood (Maegraith, 1948). In the Taveta-Pare area these processes would be of importance only in the non-immune, such as infants and young children, in whom heavy parasitaemia occurred. The development of immunity is accompanied by the production of specific humoral antibodies, such as agglutinins and opsonins, and, in particular, by a proliferation of the cells of the reticulo-endothelial system, which removes the parasites from the blood. The latter occurs chiefly in the spleen, which enlarges because of the hyperplasia and increased vascularity. The phagocytosis of red cells, however, is not entirely specific, and some normal cells may be destroyed as well as parasitized cells, though the more the immunity the greater the specificity (Taliaferro, 1949). The stagnation of blood in an enlarged spleen may of itself be a factor in causing anaemia, by the segregation of a large number of red cells from the circulation. The bone-marrow in malaria usually shows erythronormoblastic hyperplasia as a response to the anaemia, but a megaloblastic reaction has occasionally been described. It is probable, however, that the latter is due to the overstimulation of a marrow the function of which is already disordered. Depression of leucopoiesis, affecting particularly the granulocyte series, is well recognized, and the findings here are in agreement with this.

Anaemia is widespread in tropical Africa, but the importance of malaria in its aetiology is disputed. Jordan (1954) and Welbourn (1955), in East Africa, considered it to be a cause of anaemia in infants, but Garnham (1949) found only a small effect. In West Africa, McGregor and Smith (1952) and Hendrickse and King (1958) incriminated malaria, but McGregor *et al.* (1956), who compared protected and unprotected infants, found little difference between the mean haemoglobin levels of the two groups at 3 years of age. There have been few recorded observations of the effects of malaria in causing anaemia in adults who have acquired some immunity to the parasite. Macdonald (1939), in Assam, where malaria was hyperendemic, found that the response of anaemic women to iron therapy was increased by previous treatment with mepacrine hydrochloride. Foy and Kondi (1957, 1958) and Foy *et al.* (1958) discount the effect of malaria, and thought that the anaemia of warm lowland areas is mostly due to iron deficiency, from poor absorption and dermal losses, combined with the losses of menstruation or childbearing in women. They point out that the iron liberated by destruction of the red cells in malaria can be used again by the body, and that malaria would not cause anaemia unless superimposed on an already strained haemopoiesis. It is important therefore, in assessing the effects of malaria, to consider not only the degree of its endemicity but also the nutritional background. Variations in the latter may account for some of the different views expressed.

In the Taveta-Pare area anaemia was common before malaria control. That malaria had some part in its causation is shown by the changes in haemoglobin levels that have followed control. Some of the increase may have been due to the general rise in living standards. The greatest increases have been in infants and young children who had not yet acquired much immunity, but it is interesting that the relative immunity shown by older children and adults was maintained at some cost. After three years of control the haemoglobin in most children and in adult males approached levels regarded as physiologically normal (Wintrobe, 1956); but in other children, and in females during adolescence and the reproductive period, there remained some anaemia, probably due to iron deficiency.

Summary

Estimations of the haemoglobin levels of the same group of people in a part of East Africa were made before and during a successful malaria-control scheme. They were compared over the same period with a near-by non-malarious group and with another group in which malaria remained uncontrolled.

The fall in the human malaria indices was accompanied by a progressive rise in the mean haemoglobin levels. The greatest increases were in infants and young children and the least in girls and young adult females.

These changes were probably directly due to the reduction in malaria transmission, but a general rise in living standards throughout the period of observation may have had some effect.

There was also a small rise in mean total white-blood-cell counts.

The pathogenesis of anaemia in hyperendemic malaria is discussed.

I thank Dr. D. Bagster Wilson and Dr. H. Foy for helpful criticisms of the work.

REFERENCES

Dacie, J. V. (1950). *Practical Haematology*. Churchill, London.
Draper, C. C., and Smith, A. (1957). *Trans. roy. Soc. trop. Med. Hyg.*, **51**, 137.
—— —— (1960). Ibid. In press.
Foy, H., and Kondi, A. (1957). *J. trop. Med. Hyg.*, **60**, 105.
—— —— (1958). *Trans. roy. Soc. trop. Med. Hyg.*, **52**, 46.
—— —— and Sarma, B. (1958). *J. trop. Med. Hyg.*, **61**, 27.
Garnham, P. C. C. (1949). *Ann. trop. Med. Parasit.*, **43**, 47.
Hendrickse, R. G., and King, M. A. R. (1958). *Brit. med. J.*, **2**, 662.
Jordan, P. (1954). *E. Afr. med. J.*, **31**, 143.
Macdonald, G. (1939). *Indian J. med. Res.*, **26**, 1001.
McGregor, I. A., Gilles, H. M., Walters, J. H., Davies, A. H., and Pearson, F. A. (1956). *Brit. med. J.*, **2**, 686.
—— and Smith, D. A. (1952). *Trans. roy. Soc. trop. Med. Hyg.*, **46**, 404.
Maegraith, B. (1948). Ch. 3 and 10 in *Pathological Processes in Malaria and Blackwater Fever*. Blackwell, Oxford.
Smith, A., and Draper, C. C. (1959). *E. Afr. med. J.*, **36**, 99, 629.
Taliaferro, W. H. (1949). In *Malariology*, edited by M. F. Boyd, Vol. 2, chap. 39. Saunders, Philadelphia.
Welbourn, H. F. (1955). *J. trop. Pediat.*, **1**, 98.
Wintrobe, M. M. (1956). *Clinical Hematology*, 4th ed. Lea and Febiger, Philadelphia.

Medical Memoranda

Outbreak of Dysentery Caused by Shigella boydii 4

In Britain dysentery is almost entirely caused by *Shigella sonnei* and only a small amount by *Sh. flexneri*, but from time to time outbreaks are associated with the more unusual shigella types; this communication describes one such outbreak, the cause of which was found to be *Sh. boydii* 4. In a personal communication Dr. K. Patricia Carpenter, of the Dysentery Reference Laboratory, Colindale, states that the *Sh. boydii* subgroup is not indigenous to Britain, and infections caused by the various Boyd types are always "imported" —that is, either the patient himself or a contact has been infected outside this country. Over a nine-year period, up to 1958, the records of the Dysentery Reference Laboratory show that only 37 *Sh. boydii* strains are known to have been isolated in Britain, and of these only 2 were *Sh. boydii* 4 (P274); both these organisms came from patients known to have been infected abroad. An outbreak of dysentery in this country caused by *Sh. boydii* 4 is therefore noteworthy.

CLINICAL NOTES

In May, 1958, seven children, all from one family and all below the age of 9 years, were admitted to an infectious diseases hospital near Glasgow, suffering from what was described as mild dysentery; their parents are reported as not being affected. On admission the children were found to have mild diarrhoea, with no blood or mucus in the stools, and no fever; no chemotherapeutic treatment was given, and after two weeks in hospital they were discharged home. During their stay in hospital, bacteriological examination of faecal specimens revealed that all the children were excreting an organism which behaved biochemically like a shigella, but which was not one of the serotypes commonly found in this area (*Sh. sonnei*, *Sh. flexneri* 1, 2, and 3, and X variants). A few days after the seven children had been discharged home, their maternal uncle and his two children, aged 4½ and 2½ years, were admitted to hospital suffering from dysentery. From the faeces of these three were isolated organisms which appeared to be the same as those obtained from the seven children. These three patients were well within a few days, and were discharged home seven days after entering hospital.

BACTERIOLOGICAL FINDINGS

The 10 strains isolated appeared to be identical—two were selected for detailed examination; one was from one of the seven children first admitted to hospital and the other from their uncle. Both produced identical biochemical reactions —namely, acid without gas was formed from glucose and mannitol within 24 hours; from sorbitol and rhamnose a faint acid reaction was produced after three days, while maltose showed a slight acid reaction after 15 days: the tests for motility, indole, H_2S formation, citrate utilization, gelatin liquefaction, and urease formation were all negative; the Voges-Proskauer test was negative and the methyl-red test was positive. After 30 days' incubation negative reactions were obtained with lactose, sucrose, inositol, raffinose, xylose, galactose, dulcitol, salicin, and adonitol.

Slide-agglutination tests with the two strains under investigation against all the shigella antisera issued by the Standards Laboratory showed positive results with a polyvalent *Sh. boydii* serum (serotypes 1–7), *Sh. boydii* 4, and *Sh. boydii* 1. Tube-agglutination tests with these antisera produced full titre agglutination with the polyvalent boydii and the individual *Sh. boydii* 4 sera, but agglutination to only a titre of 1/10 with *Sh. boydii* 1. (Dr. Carpenter states that this agglutination with *Sh. boydii* 1 is almost certainly due to minor alkalescens–dispar group relationships.) Rabbit antisera to the two strains under test were prepared using boiled vaccines. Both sera gave a titre of 1:6,400 against boiled suspensions of the homologous strain, the heterologous strain, and also a known strain of *Sh. boydii* 4 (NCTC 8214). Reciprocal and mirror absorption tests showed that both strains were identical with each other and with a classical *Sh. boydii* 4. These findings were subsequently confirmed by the Dysentery Reference Laboratory at Colindale.

COMMENT

In view of what was known about the occurrence of *Sh. boydii* 4 in this country, inquiries were made to discover if the present outbreak had a foreign source: it was learned that the children's uncle, the only adult patient, was in fact a native of Estonia, making frequent trips to this country in his capacity as a seaman. It seems reasonable to suppose that he was the vehicle by which the organism was transmitted to the children, but, as he visited several Continental ports shortly before the outbreak developed, it is impossible to be certain of the exact location of origin of the infection. It is of interest that the outbreak produced only very mild symptoms, requiring practically no treatment, and that a careful follow-up by public-health authorities showed that the infection did not extend beyond family limits.

We thank Dr. K. Patricia Carpenter, Dysentery Reference Laboratory, Colindale, London, for her help and information, and Dr. S. Henderson, Lennox Infectious Diseases Hospital, Glasgow, for his help with the clinical details. Our thanks are also due to Miss C. Smith for her assistance.

PAUL M. H. BROWNING, M.B., Ch.B.,
Bacteriologist, Counties of Renfrew, Dunbarton, and Argyll.

P. A. BOOT, F.I.M.L.T.,

JOHN S. STEVENSON, M.D., F.R.F.P.S.,
Department of Bacteriology,
Stobhill General Hospital, Glasgow.

Reviews

ARCHETYPE AND "AION"

The Collected Works of C. G. Jung. Edited by Sir Herbert Read, Michael Fordham, M.D., M.R.C.P., and Gerhard Adler, Ph.D. Volume 9, Part I. *The Archetypes and the Collective Unconscious.* Translated by R. F. C. Hull. (Pp. 462+xi; illustrated. 52s. 6d.) Part II. *Aion. Researches into the Phenomenology of the Self.* Translated by R. F. C. Hull. (Pp. 344+xi; illustrated. 32s.) London: Routledge and Kegan Paul. 1959.

Jung's hypothesis of the collective (impersonal, objective) unconscious and its mode of functioning, the archetypes, is a bold theory. Yet it is no more daring than the theory of pre-existent instincts in animals and men. The hypothesis, though lacking scientific foundation, none the less provides a more satisfactory explanation for certain psychological facts than any other at present available. We are not surprised that the body carries traces of its history, and it is to be expected that the mind, in its structure and functioning, does the same. Jung's theory in its simplest form claims that the mind, like the body, possesses a common substratum over and above personal and racial differences.

Six well-arranged sections give Jung's main writings from 1930 to 1955 on the collective unconscious. Much of it has already appeared in English, and these earlier publications have been revised by Jung himself. Some may prefer to study the unfolding of his thought chronologically; but like the empirical pioneer he is, and always has been, Jung is concerned with the stage he has now reached rather than with older ideas, many of which have been changed and expanded.

Repetition—which has its advantages—is unavoidable in a compilation like this, where a step-by-step exposition is not attempted. It should be remembered that Jung does not consider that his work on the collective unconscious has reached its final form. Others, he hopes, will continue what he has started. Perhaps the future will bring the scientific proof which some seem to value above everything. Mr. Hull's translation is first-class. About a third of the 79 plates are in colour. It was a difficult task to arrange this diverse group of publications, and the editors have done it well.

Aion means an era, a segment, of historical time. History, in Professor Jung's opinion, takes on a new aspect when considered from the standpoint of the phenomena due to unconscious processes which accompany the changes, often sudden, of conscious reason. With this approach Jung surveys the transformations which have occurred within Christianity from its beginnings to modern times. Inevitably we are profoundly influenced in everyday life by our historical Christian background and by the secular changes in Christian principles. The bewildering situation of the modern mind becomes more understandable when we recall its development, and appreciate that changes are possible only when the personal life of individuals is altered.

Jung's concept of the archetypes—that is, the contents of the collective unconscious—is central in this study of the mind's development. The archetype of wholeness, expressed as the Self, is of particular significance in explaining the numerous forms conveying the notion of wholeness which occur—for instance, in dreams. Symbols of the Self—a figure that transcends the ego personality—have been known throughout the Christian era and are fully discussed here, as the subtitle ("The Phenomenology of the Self") indicates. The word "symbol" is given various meanings in modern psychology. Jung employs it, as has been customary for centuries, to portray "the best possible description of a relatively unknown fact; a fact, however, which is recognized or postulated." The symbol possesses dynamic value when it evokes unconscious participation, and so is not merely of intellectual or aesthetic interest.

This is perhaps Jung's most profound work. The opening chapters deal with the ego, the shadow, the animus and anima as paired opposites—that is, reality is manifest in polarity. These chapters provide an informative introduction to the dynamics of symbolism and its bearing on the development and the complexity of the modern mind.

E. A. BENNET.

FRACTURE SURGERY

Fracture Surgery. A Textbook of Common Fractures. By Henry Milch, M.D., and Robert Austin Milch, M.D. With a chapter on Anesthesia by Herbert D. Dubovsky, M.D. (Pp. 470+x; illustrated. £7.) New York: Paul B. Hoeber, Inc. London: Pitman Medical Publishing Co., Ltd. 1959.

This is a well-planned book, essentially practical, and the authors have been successful in providing all the important features required by the younger surgeons in diagnosis and treatment, especially in emergency work. The compactness of the volume will appeal to many, and this has been made possible by excluding much of the detail of clinical examination, which the authors consider must now take second place to radiographic information. The omission of dislocations, except for a limited number of fracture-dislocations, may be considered a loss to the extent that there might be a tendency to neglect to consider such conditions when there is injury around a joint.

The principles of fracture-treatment taught in New York and Boston are shown to be very similar to those prevailing in most centres in Britain. The reader will find that the authors recommend those methods of treatment which are most likely to produce anatomical alignment, in the case not only of single bones, but also of small bones such as the metacarpals. Hence many methods of internal fixation are described. Küntscher's nail is popular and the indication for its use well described. Parham's band is still in use, and Lane's plates find a greater place in the treatment of comminuted fractures than is usual in Britain. First aid, reduction by many methods, and treatment of skin defects and loss are dealt with adequately. The chapter on the hand shows that Bunnell's teaching is followed. The vascular complications are described in greater detail than those of peripheral nerve injury. It is interesting to read that the authors are not averse to removal of the cruciate ligaments when there is injury to the centre of the tibial plateau. There is a considerable amount of information on somewhat rare injuries, but details of such difficult conditions as central dislocation at the hip are limited.

The book is well printed and illustrated, and should prove valuable for ready reference.

ST. J. D. BUXTON.

GLAUCOMA SYMPOSIUM

Documenta Ophthalmologica. Advances in Ophthalmology. Edited by G. von Bahr, G. B. Bietti, J. ten Doesschate, H. Fischer-von Bünau, J. François, H. Goldmann, H. K. Müller, Jean Nordmann, A. J. Schaeffer, and Arnold Sorsby. Volume XIII. (Pp. 515+xii; illustrated. Guilders 75.) The Hague: Dr. W. Junk. 1959.

The thirteenth volume of *Documenta Ophthalmologica* is one of the most useful in this valuable series, containing a full account of the symposium on glaucoma with the original contributions and the subsequent discussions held in Liège on the invitation of Professor R. Weekers in September, 1958. The symposium was a representative meeting of many of those from several countries both in Europe and America who are engaged in elucidating the many problems of this still enigmatic condition, and, as would be expected, the report makes excellent and satisfying reading.

Most aspects of the subject were exhaustively discussed: the formation and outflow of the aqueous humour (Kinsey, Bárány, François); the central-nervous regulation of the intraocular pressure (von Sallmann, Gloster); tonometry and tonography (Kronfeld, Prijot, Goldmann); the effect of adrenocortical steroids on the intraocular pressure (Linnér); the visual fields in glaucoma (Weekers, Dubois-Poulsen, Harms); and the occurrence and manifestations of the disease as seen in a clinic (Leydhecker). An able summation of the general conclusions is contributed by Goldmann.

To analyse each article would require many pages, for the volume forms indispensable reading for those interested in glaucoma; and for good measure its value is increased by three short papers on ophthalmodynamometry, scleral rigidity, and some properties of visual space.

STEWART DUKE-ELDER.

IMPLANTATION OF OVA

Memoirs of the Society for Endocrinology. No. 6. *Implantation of Ova.* Proceedings of a Conference held at the Ciba Foundation, London, on November 27, 1957. Edited by P. Eckstein. (Pp. 97+vii; illustrated. 30s.) London: Cambridge University Press. 1959.

This memoir contains the proceedings of a one-day conference held in November, 1957. It touches on many different aspects of implantation from mouse to man, and, though it is too short to provide any substantial body of information, individual papers are stimulating and indicate active fields of current work. Dr. Eckstein, Dr. Shelesnyak, and Professor Amoroso combine to survey the subject and to stress the need for the use of newer techniques in the study of implantation—microchemical analysis, histophotometry, autoradiography, etc. Such an approach is exemplified in Dr. Lutwak-Mann's paper on the biochemistry of rabbit implantation and by Professor Boyd's contribution on glycogen in early human implantation sites. Dr. Shelesnyak's paper on deciduomata in the rat must be studied in full rather than summarized; from an elaborate series of experiments evidence is produced that histamine may play an essential role in the implantation process. Professor Robson deals with anti-metabolites which affect the products of conception while causing little reaction in the mother, and found that medium doses were liable to lead to malformations. Professor Mayer summarizes the work of his group at Bordeaux on experimental delayed implantation in rats and on the natural delay which may occur during lactation. Unimplanted blastocysts were found to survive in the absence of both ovarian and adrenal hormones and will later implant if sufficient hormone is provided. Professor Mayer has shown the direct local action of progesterone in inducing implantation by injecting it into one uterine horn only.

Altogether, valuable experimental results have been obtained from the rat, but it would be unwise to generalize from them since there are morphological and physiological species differences in the interaction of the nidating egg and endometrium—for example, the rabbit or guinea-pig blastocyst apparently fails to survive delay in implantation. It is hoped that this meeting and memoir will stimulate further research on this fundamental and fascinating process.

R. DEANESLY.

LUNG-FUNCTION TESTS

Lung Function Tests. An Introduction. By B. H. Bass, M.D., M.R.C.P.(Lond.). (Pp. 72+viii; illustrated. 8s. 6d.) London: H. K. Lewis and Co., Ltd. 1959.

Now that lung-function tests are beginning to be as essential a part of the clinical assessment of patients with lung disease as are cardiac function tests in cardiology, many chest clinicians seek a readable account of the rather complex theory and practice of pulmonary physiology. They may turn to this slim volume hoping to find simplicity and relevance to clinical problems. Simplicity they will find, but it is simplicity bought at too high a cost in inaccuracy, and of relevance to clinical practice there is almost none, for this book is about tests, not about their results in diseases of various kinds. There are, unfortunately, too many inaccurate or controversial statements scattered throughout the book for one to be able to recommend it to the uninitiated student; and for the initiated it is really too simple. Further, a number of tests are recommended that are not standard practice in this country, though they are widely used in the United States. For normal values of the various tests the reader is referred to tables, but no precise reference is given, and, indeed, no such reference could be given, for, unfortunately, no such tables exist. Indeed the whole problem of the wide range of normality in pulmonary function is not discussed at all. The idea that inspired this book is admirable; it is a pity that it fails to live up to its ideal.

C. M. FLETCHER.

INTRAVENOUS CATHETERIZATION

Intravascular Catheterization. Compiled and edited by Henry A. Zimmerman, M.D., B.S. (Pp. 682+xviii; illustrated. £6 6s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

This monograph gives an idea of the vast ramifications of research which have followed the work of Forssman in Germany and Cournand and Richards in the United States, who were all appropriately recognized recently by a Nobel Prize award. Under proper precautions long intravenous catheterization is a safe procedure, and we have only now delineated the possible fields in which it may be applied with advantage to medical knowledge and to the individual patients who are so studied.

This volume is an all-American production with one chapter from Toronto, and it gives an account by

recognized experts of the application of the technique in a great variety of fields. Here the reader will find a discussion and interpretation of results in the study of congenital and acquired heart disease, pulmonary and coronary circulations, as well as of hepatic and renal blood-flow. The value of dye-circulation studies and selective angiocardiography following localized injections into selected parts of the circulation is described, and a section on the cerebral blood-flow is also included, though this technique is seldom carried out by the intravenous catheterization method.

Notable omissions are discussion of the research of the Birmingham workers on limb and splanchnic blood-flow in normal and pathological cardiac conditions. The place of intravenous catheters in the therapeutic management of anuria and other metabolic disorders such as severe diabetic coma might have been worthy of mention. Retrograde delineation of occlusion of the renal veins in the differential diagnosis of nephrotic syndromes by Milne and his associates might also have been given a place.

The chapters on the whole are adequate, stimulating, and interesting. It is a pity, however, that the section on the pulmonary circulation is so short. This is the field *par excellence* which has been so splendidly illuminated by catheterization and in which so many fascinating problems still remain. The work, however, is scholarly, and extensive key references are included in every chapter. It should be on the shelves of every medical school library. Its chapters outline much that has been achieved, without shirking mention of the difficulties which remain. Monographs in such rapidly developing fields of endeavour are apt to date very quickly, but this one at least will be a landmark in progress.

JOHN MCMICHAEL.

THE LIVER

Physiologie und Experimentelle Pathologie der Leber. By Dr. Anton Fischer. (Pp. 187; illustrated. 46s.) Budapest: Akadémiai Kiadó. Berlin: Akademie-Verlag. 1959.

This book in German on the physiology and experimental pathology of the liver comes from Budapest. After a brief description of the anatomy of the liver, the hepatic circulation is discussed. Then follows an account of the various metabolic aspects of hepatic physiology and pathology. This book is not a record of original work but a critical review of the world literature. It suffers from a failure to include sufficient discussion of important progress made in the last two years. Electron-microscopy of the liver, conjugation of bilirubin, fraction of bile acids and the plasma transaminases are some of the advances that are either not mentioned or touched on too briefly to be of value to the reader looking for up-to-date information on the liver. The problem of language will also necessarily limit the sales of this book in the United Kingdom.

SHEILA SHERLOCK.

In his *Histochemical Technique* W. G. B. Casselman provides an introduction to the principles and practice of microscopical histochemistry. He includes a selection of reliable techniques applicable to a variety of biological problems and lists of references for further reading. The book is published in the Methuen series of Monographs on Biological Subjects (pp. 205; 18s.).

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

An Introduction to Congenital Heart Disease. By Leo Schamroth, M.B., B.Ch.(Rand), M.R.C.P.E., F.R.F.P.S., and Fay Segal, M.D.(Rand). (Pp. 116+ix; illustrated. 22s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

Exploration du Cerveau Humain par Électrodes Profondes. By Michel Ribstein. *Electroencephalography and Clinical Neurophysiology.* Supplement No. 16. (Pp. 130; illustrated. NF. 30.) Paris: Masson et Cie. 1960.

Chirurgie du Côlon. By Henri Welti. (Pp. 386: illustrated. NF. 60.) Paris: Masson et Cie. 1960.

Asklepios. Archetypal Image of the Physician's Existence. By C. Kerényi. (Pp. 151+xxvii; illustrated. 30s.) London: Thames and Hudson. 1960.

Henry E. Sigerist on the History of Medicine. Edited by Félix Martí-Ibáñez, M.D. (Pp. 313+xviii. $6.75.) New York: MD Publications, Inc. 1960.

Predisposition to Postvaccinial Encephalitis. Significance of Constitution, Especially the Status Dysraphicus in the Genesis of Postvaccinial Encephalitis. By E. J. W. Keuter. (Pp. 160; illustrated. 46s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. 1960.

The Discovery of Reflexes. By E. G. T. Liddell, D.M., F.R.S. (Pp. 174+vi; illustrated. 30s.) London: Oxford University Press. 1960.

Gastric Cytology: Principles, Methods and Results. By Rudolf Otto Karl Schade, M.D.(Dunelm), M.D.(Tübingen), L.R.C.P., M.R.C.S. (Pp. 83+viii: illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1960.

Treatment of Urinary Lithiasis. Compiled and edited by Arthur J. Butt, B.S., M.D., F.A.C.S. (Pp. 577+xxii; illustrated. £8 8s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Massachusetts General Hospital 1935-1955. By Nathaniel W. Faxon, M.D. (Pp. 490+xv. 80s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1959.

Genetic Basis of Morphological Variation. An Evaluation and Application of the Twin Study Method. By Richard H. Osborne and Francis V. De George. (Pp. 204+xxii; illustrated. 48s.) Cambridge, Mass.: Harvard University Press for the Commonwealth Fund. London: Oxford University Press. 1959.

Diseases of the Skin. By James Marshall, M.D.(Lond.). (Pp. 944+viii; illustrated. 84s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

Notes on Infant Feeding. By Stanley Graham, LL.D., M.D., F.R.C.P.(Ed.), F.R.F.P.S.(Glas.), and Robert A. Shanks, M.D., M.R.C.P.(Lond.), F.R.F.P.S.(Glas.). Fifth edition. (Pp. 76. 4s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

The Principles and Practice of Chiropody. By John H. Hanby, F.Ch.S., and H. E. Walker, F.Ch.S. Second edition. (Pp. 444; illustrated. 30s.) London: Baillière, Tindall and Cox. 1960.

Essays on the First Hundred Years of Anaesthesia. By W. Stanley Sykes, M.B.E., M.B., B.Chir.(Cantab.), D.A. Volume I. (Pp. 171; illustrated. 30s.) Edinburgh: E. and S. Livingstone, Ltd. 1960.

The Rhythm Way to Family Happiness. By John P. Murphy, M.D., and John D. Laux, M.E. (Pp. 200; illustrated. 18s.) London: Staples Press. 1959.

The Reindeer (Rangifer Tarandus L.) in Denmark. Zoological and Geological Investigations of the Discoveries in Danish Pleistocene Deposits. By Magnus Degerbøl and Harald Krog. Biologiske Skrifter udgivet af Det Kongelige Danske Videnskabernes Selskab, Vol. X, No. 4. (Pp. 165; illustrated. Dan. kr. 35.) Copenhagen: Ejnar Munksgaard. 1959.

Diatoms from Afghanistan. By Niels Foged. Biologiske Skrifter udgivet af Det Kongelige Danske Videnskabernes Selskab, Volume XI, No. 1. (Pp. 95; illustrated. Dan kr. 20.) Copenhagen: Ejnar Munksgaard. 1959.

Klinische Physiologie: Aktuelle Probleme in Übersichten. Unter Mirwirkung der Schriftleitung der Deutschen Medizinischen Wochenschrift. Edited by Dr. W. A. Müller. Volume I, Part 1. (Pp. 118+iv; illustrated. DM. 23.) Stuttgart: Georg Thieme Verlag. 1960.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY MAY 14 1960

PACKAGE DEAL

The Report of the Royal Commission will be discussed by the Annual Conference of Representatives of Local Medical Committees on May 17 and 18, and by the Special Representative Meeting of the B.M.A. on May 19. The two bodies are being advised, in the first place by the General Medical Services Committee, and in the second by the Council of the B.M.A., to accept the offer of the Minister made in Parliament and amplified in his letter of April 5.[1] The Minister stated that: "Her Majesty's Government are prepared to accept the Commission's recommendations as a whole as they stand, provided that the doctors and dentists respectively for their part are ready to accept them on the same basis." The phrase "package deal" has been freely used to describe this "offer" of the Government. As the medical profession itself had encouraged the idea that some sort of review mechanism might replace the two Spens Reports as a basis for reviewing remuneration in the N.H.S. it is unfortunate that the Government was so tactless as to imply by its "package deal" offer that the settlement of a straightforward wage claim had been made dependent upon the acceptance of the majority proposal for a review body. The two matters should never have been linked in this way, and should be separately considered. But there even is now some doubt—perhaps deliberately intended—just what is meant by "accepting the report as a whole." In the recent debate in the House of Lords, Lord Taylor, speaking for the Labour Party, said he did not think anyone quite knew what this phrase meant. This was in response to observations made by the Earl of Dundee speaking on behalf of the Government, who, referring to the criticisms made by Lord Taylor, said that many of them, though not all, "were concerned with matters which have not yet been finally decided but will fall to be discussed in the *negotiations* which we hope will take place between the Ministry of Health and the professions. . . ." (Our italics.) Lord Dundee, referring to proposals to be accepted as part of the "package deal," mentioned, as the first, the Review Body—that is the Review Body recommended by the Majority Report and not the one recommended by Professor John Jewkes in his Memorandum of Dissent. Lord Dundee said that the Government would be prepared to pass on to the Review Body a recommendation that the profession should be given the opportunity to present their arguments to it orally. But this observation of his was preceded by the following statement. Repeating the Commission's observations in the report that, as the function of the Review Body would be to advise the Government, only the Government ought to have the right formally to approach it, Lord Dundee said: "That may be so, technically; but we are ready to give an undertaking that any representations which the professions wish to make to the Review Body will be passed on to it *by the Government*. . . ." (Our italics.) This is not direct access.

Many of the motions before the Conference of Representatives of Local Medical Committees and the Special Representative Meeting rightly stress this question of direct access—that is to the Review Body. We may well ask why the Government has been so anxious to force this package deal through. The teachers are fully represented on the Burnham Main Committee, which recommends what teachers should be paid; and Lord Cohen pointed out in the Lords debate that the Association of University Teachers have direct access to the University Grants Committee. As Dr. L. Fairbairn has so aptly put it in this week's *Supplement*: "We are offered a Review Body which, instead of standing between, or above, the Government and the profession, would in fact stand behind the Government, responsible to it alone and accessible only through it."

Is it that the Government fear the direct intervention of the profession in discussions on its remuneration? However distasteful public wrangles about pay may be, the profession should recognize that, had it not been for the energy and persistence of Dr. S. Wand in the negotiations which led up to the Danckwerts Award, and since, the recommendations of the Royal Commission, unsatisfactory though they may be in some respects, would most certainly have been far more unsatisfactory than they are, both for consultants and hospital staff and for general practitioners. It was the B.M.A. which had the unpleasant task of hammering away at the Ministry on the basis of promises made by Government.

The profession has learnt to be cautious about relying on promises made by Ministers of Health or Government. It has recently seen how adroitly the

[1] See *Supplement*, April 23, 1960, pp. 233 and 234.

Minister has gone back on his party's own statements about drugs for private patients. The profession has a keen memory of the refusal of a succession of Conservative Ministers of Health to accept the Danckwerts Award and the Spens Reports as a basis for negotiating pay in the Health Service. The profession itself has been so accommodating that it has not pursued this theme and has even welcomed the prospect of a Review Body. But if one goes by the number of motions on the agendas of the Conference and the Meeting next week, the profession would clearly not feel happy about the Review Body unless it can be guaranteed the right of direct access to such a body. The Government's promises to do this or that, no doubt sincerely meant, are not enough, for the good reason that they are not binding on any future Government or Minister of Health. The history of the N.H.S. should at least have taught us that.

And what about the future? In the Lords debate, Lord Moran, who has always been a strong advocate of the National Health Service, made one or two statements that must alarm those who fear for the future. "I will go on to say," he observed, "just a word about recruitment. There we have an absolutely alarming situation. A short while ago, if a boy at any of the schools thought of going in for science, his eye was probably on medicine. Now, it is about the last thing that it is on." And a little later he said: ". . . I share the doubt of Professor Jewkes when he says he is doubtful whether the Majority Report would bring an entry into medicine of the quality that we all desire. If that is the right conclusion, it is a very alarming one." Not a few will share Lord Moran's deeply pessimistic conclusions.

PERSISTENCE OF IMMUNITY

The question of how long the body continues to respond to an antigenic stimulus was discussed recently in a symposium organized by the British Society for Immunology on "The Persistence of Immunity."[1] By such responses we may mean an increased specific resistance to a microbe, or the appearance in the circulation of antibody. We may also include the increased potential to produce antibody rapidly and in greatly increased amount in response to a subsequent antigenic stimulus, or the production of immediate or delayed-type hypersensitivity. The principal challenge to thought in such discussions is the lifelong persistence of immunity against certain acute virus infections such as measles and yellow fever. In measles the use of adult serum for prophylaxis makes it certain that specific antibody can persist for many years. So, too, in influenza the epidemiological evidence of F. M. Davenport and A. V. Hennessy[2] shows that a childhood stimulus can leave its impression for as long as thirty years, for people who were old enough to have experienced the influenza virus in 1918 responded to the epidemic in 1953 by making antibody recognizably directed against antigenic components of earlier influenza variants to which younger people failed to respond. But the fact crucial to our hypotheses is whether antibody production or potential immunity can continue in the absence of antigen. Persistence of antigen is known to occur in conditions such as trypanosomiasis or leishmaniasis, and in rickettsial infections—for example, latent typhus—and in the infections with viruses—for example, herpes simplex.

Drs. H. G. Pereira and Janet F. Niven gave the symposium new and interesting data on latency of adenovirus as observed in the rabbit. Inoculation in this animal of a single intravenous dose of adenovirus type 5 is followed by an antibody response lasting up to eight months. However, by growing the spleen tissue from such animals *in vitro*, virus could always eventually be induced to appear in the cultural fluids, and such unmasking could be achieved in tissue from rabbits killed up to eight months after inoculation. Indeed, these findings seem in all ways analogous to those recorded in man for adenoviruses types 1, 2, 5, and 6 by R. J. Huebner and colleagues.[3] Serum antibodies to viruses of these types are widespread and persist often from childhood, and this accords with the frequency with which viruses of these types are found in human tonsils and adenoids.

Immunity to such virus diseases as measles and smallpox has long been interpreted in terms of humoral antibody, and this raises the question of the minimal amount which is required to sustain resistance. Dr. F. O. MacCallum discussed the evidence provided by cases of agammaglobulinaemia, which, in spite of very low levels of gamma-globulin and considerable susceptibility to bacterial infections, show virtually a normal behaviour towards virus infections. The evidence leaves us with the choice either that these low levels of antibody will suffice or that other mechanisms must be invoked to account for resistance to virus diseases. Thus mechanisms analogous to that by which interferon is produced

[1] November 27–28, 1959.
[2] Davenport, F. M., and Hennessy, A. V., *J. exp. Med.*, 1956, **104**, 95.
[3] Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H., and Bell, J. A., *New Engl. J. Med.*, 1954, **251**, 1077.
[4] Barr, M., and Glenny, A. T., *J. Hyg., Camb.*, 1945, **44**, 135.
[5] Harrison, W. T., *Amer. J. publ. Hlth*, 1935, **25**, 298.
[6] Garvey, J. S., and Campbell, D. H., *J. exp. Med.*, 1957, **105**, 361.

may be at work, or it is possible that a certain primitive immunological capacity is retained which allows the agammaglobulinaemic patient to develop delayed allergy and so to resist virus infections.

Persistence of resistance is seen outside the field of virus diseases, and Dr. Rebecca C. Lancefield carefully investigated the generally recognized fact that reinfection with a given serological type of Group A streptococcus rarely, if ever, occurs. By means of bactericidal and mouse-protection tests with sera recently collected, type-specific antibodies could be detected and correlated with past infections dating from as long as 32 years before. Such antibodies were apparently sustained without any clinical or bacteriological evidence of reinfection.

However, the possibility that repeated antigenic stimuli, naturally encountered, give rise to the antibodies in such cases forces the sceptic to insist on the use of non-living antigens. Among these, as was shown by Dr. E. A. Kabat, two divergent modes of behaviour in both man and animals are manifest. The bacterial polysaccharides after a single injection cause a slow increase of antibody to a plateau lasting five to eight months and a very slow decline over a period of years. In this period reinjection of polysaccharide has little effect on existing antibody levels. The protein bacterial toxins (for example, of diphtheria or tetanus bacilli), on the contrary, cause rises of antitoxin which rapidly reach the maximum and recede within weeks to much lower levels, and they can be recalled, often to far higher values, by further injections. This difference in behaviour is probably attributable to the ready destruction of toxins, demonstrable *in vitro*, by proteolytic enzymes, while the bacterial polysaccharides appear extraordinarily resistant to enzyme attack. The persistence of the polysaccharide antigens apparently accounts for the persistence of antibody in this case.

As to the protein antigens, the accumulated experience in animals and man at the Wellcome Research Laboratories, reviewed by Miss M. Barr, showed that the power of immune response or potential immunity is a function not only of the extent of previous stimulation but also of the time elapsing since stimulation. After primary stimulation of adequate dose the power to respond continues to increase long after the amount of circulating antitoxin has declined. M. Barr and A. T. Glenny[4] have stressed that, in order to secure eventually a maximum antitoxin response in the horse, a long period of rest (at least a year) is essential after preliminary immunization. This evidence is of practical importance in human prophylaxis, since too close spacing of injections may result in failure to give the antibody-producing mechanism sufficient reactivity (or potential immunity) to ensure that small stimuli naturally encountered continuously maintain sufficient antitoxin in the circulation. Its theoretical implication is that multiplication of immunologically conditioned cells continues long after synthesis of antibody has stopped. But, since in these studies use was made of alum-precipitated antigens, which can persist in the local granuloma for many weeks at least,[5] these data still do not allow us to conclude that such persistence of the immune response can occur in the absence of antigen.

Direct cytological evidence of prolonged persistence of a non-living antigen in the cells of the body is difficult to procure, since its demonstration with a labelled antigen may really denote merely the persistence of the label itself. However, J. S. Garvey and D. H. Campbell[6] have shown that ^{35}S-labelled haemocyanin can still be detected in liver cells of the mouse after 330 days and still is demonstrably antigenic in other animals. The sceptic will object that after the incorporation of numerous azo-phenyl-sulphonate groups into the molecules of this protein it can hardly be expected to behave like the unlabelled native protein, and we are left with the admission that satisfactory evidence for prolonged survival of simple protein antigens in the cells of the body has still to be produced.

DISINFECTING THE HANDS

There seems to be little doubt that when *Staphylococcus aureus* can be cultivated from the skin of the hand it is not usually part of the resident flora, as is *Staph. albus*, but is a passenger in a state of suspended animation which has been deposited on the skin from the places where it can multiply—that is, the nose or perineum of the individual himself, similar carrier sites on another individual with whom he has recently had close personal contact, or a septic lesion on a patient he has attended. Such staphylococci would probably disappear within two to three days of deposition,[1] but, because the supply is continually being renewed, the number present on the skin generally remains fairly constant. Thorough washing of the skin will remove many of the *Staph. aureus* reaching it in this way, and when this washing is followed by immersion of the hands in 70% alcohol it may no longer be possible to cultivate these organisms. Nor do they always reappear when sweating is induced by wearing rubber gloves and immersing the hands in hot water. *Staph. aureus* on

the hands of 10 out of 15 subjects behaved in this way.[2] Nevertheless, sweating may be accompanied by the reappearance of *Staph. aureus* on the surface of the skin, so that quite large numbers may be found in the gloves after they have been worn for some time.

The reasons for the differences in bacterial behaviour still await elucidation. It is improbable that individuals whose *Staph. aureus* organisms reappear on the hands when sweating are true hand carriers in the sense that the organism has become established as part of the resident flora and is multiplying in the sweat glands, hair follicles, and deeper layers of the corium. If this were so, one would expect fairly often to encounter individuals from whose hands large numbers of *Staph. aureus* could always be cultivated but who are not nasal or perineal carriers. Yet this virtually never occurs, it being an almost invariable finding that it is only nasal or perineal carriers who have heavily contaminated hands, and their hands become free as soon as they cease to be carriers in the nose or perineum. It would therefore seem probable that the *Staph. aureus* organisms which reappear when sweating is induced are passengers which have found their way into the deeper layers of the skin and are carried to the surface in the flow of sweat. Nevertheless, it is still possible —though not yet proved—that some apparently normal persons may have hands whose skin is actually parasitized by *Staph. aureus*. Such persons would probably contaminate the interior of their gloves much more heavily.

So long as *Staph. aureus* remains within the glove, it cannot do very much harm, but gloves are punctured sufficiently often in the course of operations to suggest that oozing of their contents into the wound may be responsible for some cases of post-operative infection.[3] If, therefore, the skin itself or the interior of the glove is treated with a compound that can kill *Staph. aureus*, this particular hazard would be greatly reduced. Until recently no suitable compound has been available, largely because it must not be injurious to either patient or surgeon even when used for long periods every day. Some of the newer antiseptics now available meet these specifications and have accordingly been investigated by Dr. E. J. L. Lowbury and Mr. H. A. Lilly, whose paper is published in the opening pages of this journal. They employed for this purpose a technique which closely mimics the conditions in which such compounds would be required to act, and determined not only the number of organisms of all kinds present in gloves after being worn for one hour but the number oozing out of holes when tested under standard conditions. These experiments showed that much might be achieved by immersing the hands for three minutes in 70% alcohol after the usual scrubbing process. The total bacterial counts obtained from the interior of the gloves after having been worn for an hour were only one-twentieth of those obtained when the alcohol bath was omitted. Since pre-operative treatment with alcohol which is allowed to evaporate before the gloves are put on cannot play very much part in killing organisms that reach the glove cavity when sweating occurs, it is not, therefore, very surprising that still greater reductions were obtained when the skin itself was covered with a film of hexachlorophane, "phisohex," or chlorhexidine applied in various ways, or alternatively the glove cavity contained a dusting powder consisting of a mixture of neomycin and bacitracin.

It is a matter of some importance that in these experiments the behaviour of *Staph. aureus* was not specifically investigated, but in the second part of their investigations, which concern the effect of antiseptics on the flora of nurses' ungloved hands, Lowbury and Lilly estimate the numbers of this organism before and after treatment. Here, too, an effort was made to mimic as closely as possible the conditions in which antiseptics applied to the hands of nurses would be required to act. On the whole the results were disappointing in that total removal of *Staph. aureus* could not be effected by methods that are practicable for everyday use. Nevertheless, the use of hexachlorophane soap for all ablutions did effect some reduction (about 50%) and was certainly better than when this soap was used only on duty in the wards or when chlorhexidine cream was applied three or four times a day.

Thus, although the new antiseptics may reduce contamination of the hands by *Staph. aureus*, it would seem to be improbable that they are sufficiently powerful to eliminate this organism altogether. For this reason another approach might be to determine the number of *Staph. aureus* in gloves after use in operating theatres as a guide to determining whether the surgeon or nurse can safely continue to work in the theatre. A second measure worth consideration is to extend the wearing of gloves by nurses in the wards. *Staph. aureus* that would otherwise have reached their hands will get on to the gloves instead and can be readily and easily removed, while the *Staph. aureus* from their own nose or perineum that may be present on their hands will be imprisoned within the gloves—so long as they remain intact.

[1] Ricketts, C. R., Squire, J. R., and Topley, E., *Clin. Sci.*, 1951, **10**, 89.
[2] Gillespie, E. H., Devenish, E. A., and Cowan, S. T., *Lancet*, 1939, **2**, 870.
[3] Devenish, E. A., and Miles, A. A., *ibid.*, 1939, **1**, 1088.

RHYTHMIC SENSORY STIMULATION

Regular repeated stimuli applied to almost any sense organ—whether eye, ear, skin, or muscle spindle—cause various changes in the reactions of the organism as the sequence progresses. The changes do not always represent the diminishing response that the terms habituation or adaptation would suggest. In man's consciousness the effect may vary from the maddening to the monotonous, as shown by the irritation of a dripping tap on the one hand and the soothing of a lullaby on the other.

In physiological experiments stimulation of the subject by flickering light may produce spike-and-wave effects in the electroencephalogram or even a clinical fit. An apparently opposite effect is the induction of sleep by slow electrical stimulation of the hypothalamus.[1] It is tempting to compare these cumulative effects with those of small repetitive stimuli on oscillating physical systems, but unfortunately proof that reverberating circuits exist in the central nervous system is still lacking. In general, stimuli applied in slow rhythms and at low intensity diminish excitation, while those applied in rapid rhythms and at high intensity increase it. However, paradoxical results can occur, as is shown dramatically by Dr. Ian Oswald's experiments reported at p. 1450 this week. His subjects went rapidly to sleep though exposed to intense synchronous rhythmic music, electric shocks to a limb, and flashing lights to eyes glued open. As Oswald stresses, the effects of rhythmic stimuli depend not only on their nature—rate, loudness, complexity—but also on the state of the organism at the time of stimulation and the number of ways open to it to react. H. S. Liddell[2] pointed out that Pavlov neglected the importance of the restraining effects of the animals' harness in his conditioning experiments for the production of the breakdown of adaptive behaviour ("experimental neurosis"). Oswald's long-suffering but presumably well-motivated volunteers stuck it out, and went to sleep rather than walking out of the situation in more direct ways.

Much has been learned about the physiology of sleep in recent years, so that the idea of sleeping and waking centres has been replaced by the concept of vigilance. This is held to be a subtle and infinitely graduated continuum of cerebral excitability that is mainly regulated by the central reticular substance in the region of the mid-brain. As Oswald, B. Bjerner,[3] and others have found in normal subjects under special circumstances, vigilance may be lowered so that the person seems by various criteria to sleep, and yet this condition lasts for a few seconds only. The brief periods of sleep experienced by patients in narcolepsy are identical physiologically. A positive or active state of inhibition has often been postulated to account for sleep and in general for reduction of vigilance, but this proves to be an elusive and equivocal concept when applied to a complex nervous system. Inhibition as a physiological state more or less the converse of excitation is found at the neuronal or synaptic level, but it has not clearly been proved to exist at higher levels in the sense that Pavlov and some neuropsychologists have used it. (The Freudian use of the term is different again.) On the inhibition theory sleep was assumed to result from "deafferentation," a diminution and "monotonizing" of the sensory inputs. But the higher centres make an important contribution, for electrical stimulation of certain areas of the cortex arouses the subject. Of relevance too are the clinical problems posed by the resistant insomnia of neurotic, tense patients. There is clear evidence of a central controlling or selective mechanism working downwards on the sensory inflow; this mechanism may effect differential attention to competing stimuli and more purely psychological factors such as attitude. It is possible that the concept of an excitation–inhibition dichotomy will be replaced by one of more complicated differential patterns. The apparent remoteness of these notions from the investigation of the effects of rhythmic stimuli illustrates well how difficult it still is to translate the results of physiological experiments into psychological concepts appropriate to function at higher levels.

[1] Hess, W. R., *Helv. physiol. pharmacol. Acta*, 1944, **2**, 305.
[2] Liddell, H. S., in *Personality and the Behavior Disorders*, 1944, edited by J. McV. Hunt, **1**, chapter 12. New York.
[3] Bjerner, B., *Acta physiol. scand.*, 1949, suppl. 65.

TRAVELLING FELLOWSHIPS FOR GENERAL PRACTITIONERS

Last year the trustees of the Claire Wand Fund awarded two travelling scholarships to general practitioners, thereby enabling them to examine some of the features of postgraduate education in Canada and the U.S.A. Unfortunately such opportunities for a general practitioner to go abroad for postgraduate study are few and far between. Unlike the hospital specialist, who can seek assistance from several sources, he must dig deep into his own pocket for fares, subsistence expenses, and, unless he has very amenable partners, for the salary of a locum. The cost of all this is prohibitive. Now, owing to the generosity of the Nuffield Foundation and to the initiative of the College of General Practitioners, a scheme has been devised which, over a period of four years, will enable 12 general practitioners in the United Kingdom to go abroad for six months to undertake approved postgraduate study in some subject of importance to general practice. A similar award will be made in rotation each year for a doctor from Australia, New Zealand, Canada, and South Africa. In addition assistantships are being offered so that suitable applicants can gain experience as locumtenents in the practices of the fellowship holders during their absence.

Thanks to the £50,000 contributed by the Nuffield Foundation these awards (of which details are given at p. 1516 in this issue) will cover travelling and living expenses for the successful applicants and their wives, and a sum of up to £750 for the locumtenent. A scheme of this sort has long been wanted, for it will not only be an encouragement to general practitioners in Britain, but it will also give some of our colleagues overseas an opportunity to meet a being they can hardly believe exists, a real family doctor.

TRAINING IN RADIOLOGICAL HEALTH AND SAFETY

The Fleck Committee appointed by the Prime Minister to investigate the accident to No. 1 Pile at Windscale in October, 1957, drew attention in their report[1] to the urgent need for specialists trained in the principles and techniques of radiological protection. They recommended that the Atomic Energy Authority should take the lead in meeting this need, and the Authority therefore appointed a Committee on Training in Health and Safety under the chairmanship of Sir Douglas Veale. The comprehensive report[2] which this committee has just issued estimates the type and numbers of staff likely to be needed in this field during the next ten years and describes the best ways of training them. It classifies the staff needed into categories A, B, and C. Briefly, these categories may be described as honours graduates, technically qualified staff, and supporting staff. The committee estimates that some 200 workers in category A, 300 in category B, and 600 in category C will be needed over the next decade. The largest single employer will be the Central Electricity Generating Board, with 50 in category A, 60 in B, and 250 in C. The remainder will be distributed among a host of Government departments, local authorities, public corporations, and industrial firms, large and small. The larger undertakings, like the Central Electricity Board, need specialists capable of taking responsibility for important decisions, whereas a small firm may require only sufficient knowledge among its own staff to recognize which problems can be dealt with by routine methods and which require expert advice and assistance.

To make the best use of highly trained staff the committee recommends the establishment of a National Radiological Advisory Service, organized on a regional basis, which would provide both advice and technical assistance to departments and firms requiring it. Such a service would be linked with the universities, regional hospital boards, local government departments, and with the industry in the region. It would incorporate the existing Radiological Protection Service set up some years ago by the Medical Research Council and the Ministry of Health, and would carry on the activities of this organization within the larger framework.

Turning to methods of training, the Veale Committee rejected the suggestion that the Atomic Energy Authority should establish "a national training centre for health physics and nuclear safety staff." Inquiries showed that the universities and technical colleges were willing to assume responsibility for the new training schemes required. Some universities have already begun to train staff destined for category A posts by means of special courses leading to the M.Sc. degree or by providing research facilities leading to the Ph.D. From a long-term point of view this is undoubtedly the best way of securing staff of the necessary calibre to fill these posts. The urgency of the Fleck Committee's recommendations must not, however, be lost sight of, and if the universities and technical colleges are to carry this load they will presumably require some extra resources in money and staff.

The Veale Committee recognized that the hospital service already possesses the necessary specialist staff—radiologists, physicists, and radiographers—and that any necessary increase in numbers can be met by the present internal training schemes. The report points out, however, that conditions of service may have to be made more attractive in order to maintain recruitment in face of increasing competition. Other recommendations of interest to the medical profession are that radiological health and safety should be taught to students taking the D.P.H., and that the basic medical curriculum might include enough instruction in the use and hazards of ionizing radiation to give a clear picture of the scientific principles involved and the significance of the effects.

[1] See annotation, *Brit. med. J.*, 1958, **1**, 151.
[2] *Training in Radiological Health and Safety*, 1960. H.M.S.O., London. Price 5s. 6d. net.

GIFTS TO THE ZOO

As the pressure of man on wild country increases in every continent, so does the importance of preserving some species of animals and plants which are thus threatened with extinction. The genetic combinations represented in highly developed species are irretrievably lost if the species is extinguished, and there are strictly utilitarian as well as many other reasons for wishing to prevent that. The great zoological gardens of the world play their part here, foremost among them being the London Zoo and its offshoot at Whipsnade. Moreover, the London Zoo has for many decades been a centre of active research into animal anatomy and physiology. Nor should we forget its other and important function of introducing uninstructed visitors, especially children, to the extraordinary variety of living creatures.

As a recipient of large charitable gifts the London Zoo has perhaps been somewhat neglected, so that recent donations deserve a special welcome. The donation of £250,000 by Mr. Jack Cotton, an industrialist, is much the largest ever made to the Zoo. It will permit some badly needed modernization to be carried out. The Nuffield Foundation, turning for a moment from the vast gifts it has bestowed for the advancement of clinical medicine, has now given the Zoo £100,000 to found an institute of comparative medicine and to provide two senior research fellowships. Thirdly, the Ford Foundation, another immense benefactor, has given $550,000 (£196,000) to endow a series of research fellowships in animal reproduction. Under Sir Solly Zuckerman, its honorary secretary, the Zoo has received much encouragement to develop its scientific side. These gifts will be a great help in developing the services there that many anatomists and physiologists find indispensable.

The next session of the General Medical Council will open on Tuesday, May 24, at 2.15 p.m., when the President, Sir David Campbell, will take the chair and will deliver an address.

Drug Treatment of Disease

INFECTIONS OF THE EAR

BY

COLIN M. JOHNSTON, M.S.

Otologist, Swindon and Cirencester Hospitals

ACUTE OTITIS MEDIA AND MASTOIDITIS

The introduction of a widening range of antibiotics in the past fifteen years has profoundly altered the treatment of acute otitis media, greatly altered the need for surgery, and diminished the incidence of intracranial spread of infection and permanent deafness. It is also agreed that the virulence of otitic infections has undergone a change, so that to-day we do not see some of the devastating infections prevalent years ago. During this time there has also been a realization of the dangers of antibiotic therapy, and, while the need for early treatment in adequate dosage and the continued necessity for surgical drainage of pus is now widely known, the delayed effects in causing deafness and cholesteatoma are not yet generally realized or accepted. It is easy to place too much reliance on drugs and to delay surgery; this is dangerous, because it ignores basic surgical principles and may lead to catastrophe. The indications for advising surgical intervention may be slight and often require more judgment and experience than was formerly the case.

Acute aural infections may be caused by a variety of organisms whose identity cannot be determined by the clinical features alone. Moreover, the bacteriology may from time to time present considerable variation, not only in the type of infecting organism but in the virulence and drug resistance of a particular organism. Thus Hodgkin (1957) found that more than half (in winter, more than two-thirds) of his cases of acute suppurative otitis media were due to *Streptococcus pyogenes*, but Friedmann (1954) a few years earlier found this organism to be responsible in less than a quarter of his cases. Recently there has been an increase in the proportion of cases infected with *Staphylococcus aureus*, and in many this organism is resistant to some or all of the antibiotics in common use. Because of the variability of the virulence and antibiotic sensitivity of the organism and the natural resistance of the patient—the latter includes the antibody response as well as local factors such as adenoidal hypertrophy, the functioning of the Eustachian tube, and the anatomical configuration and scarring from previous infections in the middle ear and mastoid process—the choice and method of administration of the antibiotic are dictated by the clinical findings and the bacteriological investigation.

Mild Infections

In the case of a mild infection of the middle ear with little systemic reaction seen 12 to 24 hours after the onset of pain and by then showing only slight injection of the drum and minor loss of hearing to the whispered voice, it is possible that resolution will occur promptly with rest in bed, acetylsalicylic acid, and local heat. In the opinion of many, however, it is usually more prudent to treat such a case with sulphonamides or an antibiotic. The choice of sulphonamide drug is wide and open to personal choice, but a good choice is sulphadimidine 3 g. initially, followed by 1 to 1.5 g. subsequently every six hours.

For children the dose should be approximately one-third of the adult dose from 1 to 3 years of age, half the dose from 4 to 10 years of age, and two-thirds of the dose from 11 to 15 years. Unless considerable improvement is obvious after 24 hours this treatment should be discontinued and an antibiotic administered. When the onset of the ear infection is associated with more pronounced general and local manifestations, an antibiotic should be used initially and no reliance placed on a sulphonamide alone.

Penicillins

The object of treatment with an antibiotic is to obtain a rapid concentration in the blood sufficient to exert a bactericidal or bacteriostatic action, depending on the drug used and the antibiotic sensitivity of the invading organism. Penicillin is bactericidal as well as bacteriostatic, and though its spectrum of activity is narrow it is the drug of first choice in middle-ear infections provided the infecting organism is sensitive and the patient has not shown a sensitivity reaction to the drug.

Except in the most severe infections penicillin is usually given by itself but may be combined with a sulphonamide. In pyogenic infections penicillin should be given as soon as possible so as to prevent the formation of pus. Once the middle-ear cleft contains frank pus or even flakes of pus floating in an inflammatory exudate and the drum remains intact, there is a risk that adhesions will form and cause residual deafness. It is probable that this sequela is more likely after infections treated with sulphonamides.

Some otologists advise routine myringotomy to effect drainage in all cases of suppurative otitis, and there is no doubt that this operation should be carried out whenever resolution is delayed.

Penicillin may be given by the intramuscular route as benzylpenicillin (crystalline penicillin G) 500,000 to 1,000,000 units two to four times daily (250,000 to 500,000 units for a child). A long-acting penicillin such as procaine penicillin or benethamine penicillin may be added in doses of 300,000 to 500,000 units but tends to be more potently allergenic than the crystalline salts. Penicillin can also be given by the oral route either as phenoxymethylpenicillin (penicillin V) in the form of tablets, capsules, or suspension, 250 mg. for adults (125 mg. for children) or benzylpenicillin, 600,000 units for adults, half an hour before a meal at intervals of not more than four hours. A "loading" dose of benzylpenicillin, 1,000,000 units for the adult, should always be given at the outset of a course of oral treatment and preferably once a day afterwards.

The penicillin levels in the blood obtained by oral administration are satisfactory in infants up to the age of 1 year, but with increasing age considerable variation is found, though the levels tend to be more satisfactorily

maintained in children. Many general practitioners find the oral route gives satisfactory results, and it has the advantage of ease of administration. However, some patients will not keep to the prescribed times for taking the drug, and for this and other reasons satisfactory blood levels are not maintained. Delayed resolution resulting in deafness or partial control of the infection, possibly resulting in intracranial spread of the infection, may ensue, and many otologists having to treat such "failures" are strongly of the opinion that oral penicillin therapy should not be used for this disease.

Streptomycin

Streptomycin has a synergistic activity when given with penicillin. Intramuscular injections of 500 mg. combined with 500,000 units of penicillin will often control an infection when penicillin alone has failed. However, its use in otitis media may not be without danger to the hearing in view of the well-known toxic effect on the auditory nerve.

Ear Drops

Should the ear drum perforate during the course of the infection every effort must be made to prevent secondary bacterial invasion from the external auditory meatus. When rapid resolution is taking place no local medication is required, but, if necessary, ear drops containing a non-irritating, broad-spectrum antibiotic may be instilled. Syringing or dry-mopping of the deeper part of the meatus is not advisable within the first few days of the appearance of the discharge owing to the risk of introducing fresh infection, but thereafter there is no harm in prescribing ear drops containing polymyxin, bacitracin, or neomycin. These antibiotics are not antagonistic to penicillin, as are the tetracyclines (Jawetz *et al.*, 1958). Penicillin drops should never be used owing to the high risk of causing a local skin reaction and suprainfection with resistant organisms.

In most cases, therefore, provided the patient has never previously shown any signs of reaction to the drug, treatment should be started with systemic and possibly oral penicillin. If the ear is already discharging, a swab should be taken for bacteriological examination if laboratory services are available. By the time a report is received the effects of the initial treatment will be apparent and can then be modified if necessary according to the antibiotic sensitivity of the organism found. Here it may be mentioned that intensive treatment with penicillin will sometimes succeed despite a report of a penicillin-resistant organism, and there is no harm in persisting for another 24 hours at least if clinical examination shows an immediate and dramatic response to penicillin therapy.

Tetracyclines

When the use of penicillin therapy is contraindicated, other antibiotics must be used, preferably in the light of the bacteriological findings. The next in order of preference is one of the tetracyclines—chlortetracycline ("aureomycin"), oxytetracycline ("terramycin"), or tetracycline ("achromycin") in doses of 250 to 500 mg. every six hours. For children the usual dose is 2.5 to 7.5 mg. per kg. body weight every six hours.

Vitamins

Vitamins, especially those of the B group and K, may be given concurrently to prevent deficiency arising from alteration in the bacterial flora of the gut. Suitable preparations are tab. aneurin. co. fort. B.N.F., 2 tablets thrice daily, and tab. acetomenaphthon. B.P. (vitamin K), 5 mg. thrice daily.

Because the virulence of the organism cannot always be judged at the onset, and because early thrombophlebitis may occur in the bone surrounding the middle-ear cleft, those antibiotics which are bacteriostatic only (e.g., the tetracyclines) are slower in their bacteriological effect and are less likely to overwhelm the infection before necrosis of bone has occurred. It is the author's experience that mastoid surgery has to be undertaken more commonly for cases treated initially with the tetracyclines than those treated with penicillin.

Use of other antibiotics, particularly erythromycin, is not recommended in the conditions of general practice, and, if a case is not rapidly responding to treatment as shown by subsidence of pyrexia, toxaemia, pain, and tenderness, diminution of the discharge and the inflammation of the drum, together with some return of hearing, removal to hospital is indicated. It follows that if treatment is started several days after the onset of the disease, particularly if the ear is already discharging, considerable discretion is required in deciding for how long one is justified in continuing antibiotic treatment.

CHRONIC OTITIS MEDIA

Two Varieties

A distinction must be made between the benign and the severe varieties. In the former the condition has been preceded by the manifestations of acute otitis media; an odourless mucoid or mucopurulent discharge flows through a clear-cut central perforation of the membrana tensa, and formation of granulation tissue or polyps is rare. The cause of the chronicity usually lies outside the middle-ear cleft and is due to ascending infection from the nasopharynx or entrance of infection via the meatus through a pre-existing perforation of the drum.

In the severe variety the disease essentially lies in the middle ear or mastoid and often has an insidious onset. A purulent, offensive discharge seeps through a perforation in the edge of the drum or through Shrapnell's membrane. Granulations are common, the incus or body of the malleus is usually necrosed, and the mastoid air cells are absent or partially formed. Cholesteatoma may be present. Resolution can occasionally occur with frequent and scrupulous cleansing, but such a result is generally only temporary, and at best carries a risk of deafness and at worst the possibility of serious or fatal intracranial complications. Thus surgery is advisable in most cases, and drug treatment will not be discussed. However, if there is delay before operation is undertaken, the discharge will be less unpleasant and possibly diminished if aurist. spiritus (50% alcohol in water) is instilled twice daily.

First Essential

For benign chronic otitis media the first essential is treatment of the predisposing causes and removal of decomposing debris from the meatus. Instillation of drops or powder containing an antibiotic will control the entrance of fresh infection, and one having a wide spectrum of activity should be chosen. The meatal skin is often irritated by the middle-ear discharge and is then

more readily sensitized by the preparation used, thus increasing the bacterial swarm.

Penicillin should never be used. Chloramphenicol rapidly sterilizes the area but will almost certainly be followed by a skin reaction if used for more than two to three weeks. There are, however, numerous proprietary preparations containing the tetracyclines, neomycin, bacitracin, or polymyxin in varying proportions which have a broad spectrum and only rarely cause sensitivity even after prolonged use. Some also include a hydrocortisone derivative and can be employed with advantage if there is an obvious otitis externa.

These preparations are at present expensive, but their use is justified in the speed with which infection is brought under control. It is probably true that treatment can now be completed in days compared with weeks taken in the pre-antibiotic era.

OTITIS EXTERNA

The acute diffuse form is less common in Great Britain than in warmer climates, and tends to occur in summer and after bathing. Because of the extreme tenderness and swelling of the meatal skin, pus and debris have to be removed gently; this care will avoid abrading the surface and exacerbating the infection. A wick of "selvedge" gauze, ½ in. (1.3 cm.) wide, soaked in 10% glycerin and ichthammol inserted deeply into the meatus and changed daily, will relieve the pain and remove pus and debris.

When the swelling subsides the meatal walls can be painted with 1 or 2% crystal (gentian) violet in alcohol/water solution. Alternatively an ointment in a water-miscible basis containing hydrocortisone and a wide-spectrum non-sensitizing antibiotic can be inserted with a fine wool-tipped probe twice a day.

It should seldom, if ever, be necessary to incise a furuncle of the external meatus, and the treatment described above is usually sufficient. Systemic antibiotics may be given, but many consider that their use predisposes to a second attack a few weeks later and should therefore be reserved for the relapsing case.

Scratching

Chronic otitis externa is associated in at least a third of the cases with seborrhoea of the scalp, and, while energetic treatment to the ear will temporarily clear the condition, relapse is likely unless the scalp is treated at the same time. Subsequent neglect of the scalp will predispose to relapse of the otitis. In a few individuals emotional strain will precipitate an attack, and complete resolution of the otitis will not occur until the anxiety has been overcome.

As local irritation is usually the first symptom to appear and the last to disappear with treatment, exacerbation of the lesion from scratching is commonly found unless the patient is warned. If the finger-nail is used, excoriation and weeping will be confined to the concha and may spread to the surrounding skin. Occasionally a hair clip or the side-piece of a spectacle frame may be used in the meatus.

Removal of Debris

Removal of epithelial debris is an essential part of the treatment. In some cases there is a pronounced hump on the bony meatal floor forming a "gutter" against the lower margin of the tympanic membrane. Daggett (1942) stressed that until epithelial debris, which may not be visible because of the hump, is removed and the gutter subsequently kept clean, the otitis will not resolve.

Removal of debris is best carried out by dry mopping under direct vision with fine straight and bent wool-tipped probes. Gentleness is essential to avoid pain and additional trauma. Alternatively, syringing may be carried out provided the meatus is carefully dried afterwards. The inflammation and infection can then usually be controlled by application of 1% hydrocortisone and a broad-spectrum antibiotic and is the treatment of first choice. Initially, an ointment with a water-miscible base is preferable, because aural drops tend to keep the surface layers of epithelium sodden. Later a change may be made to a greasy base, though this is often not required. Most patients may be taught to use a probe tipped with the minimum of cotton-wool, first to remove debris and then to apply a thin smear of the ointment. A suitable probe can be made from a wire paper clip which has been straightened and a series of nicks to grip the wool tip made near one end with a fine file or wire cutters.

Treatment should be carried out at least twice a day. Alternative preparations are too numerous to mention here, but 2% crystal violet in 50% alcohol/water solution, 0.1% thiomersal ("merthiolate") in water or as the tincture in alcohol, acetone, and water, or aurist. alumin. acetat. B.N.F. are useful.

Sensitization

The meatal skin is probably more readily sensitized to drugs than other parts of the body. Most drugs can cause trouble, but some, such as neomycin and the tetracyclines, rarely do so and usually only after continuous application for several weeks. Particularly with neomycin the reaction may be so mild, and in addition be modified by hydrocortisone applied at the same time, that it passes unrecognized. Unsatisfactory progress after two to three weeks' treatment should therefore be an indication to change the therapy, either to another antibiotic or to another substance. Dermatologists have for long held that penicillin should never be applied in an ointment or lotion to the skin, and the author wishes to support this view most strongly in relation to otology.

Experience with chloramphenicol has shown that, while it is efficient at controlling a wide range of bacterial infections, continued use in the ear for more than two to three weeks will result in an acute skin reaction in almost all cases. Furthermore, such sensitivity will persist for several months. There are also considerable advantages in using antibiotics which are not given systemically, such as neomycin, polymyxin, and bacitracin, to avoid the development of drug-resistance to bacteria that may cause a more serious infection. Some patients may become sensitized to propylene glycol, which is used as the vehicle for most antibiotic ear drops.

REFERENCES

Daggett, W. I. (1942). *J. Laryng.*, **57**, 427.

Friedmann, I. (1954). In *Modern Trends in Diseases of the Ear, Nose and Throat*, edited by M. Ellis. Butterworth, London.

Hodgkin, K. (1957). *Lancet*, **2**, 514.

Jawetz, E., *et al.* (1958). Quoted in *The Extra Pharmacopoeia (Martindale)*, 24th edition, 1, p. 1402.

DETERMINATION OF THE AGE/SEX STRUCTURE OF GENERAL PRACTICE POPULATIONS

(A BASIC REQUIREMENT FOR EPIDEMIOLOGICAL RESEARCH IN GENERAL PRACTICE)

A REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR COMMITTEE FOR RESEARCH IN GENERAL PRACTICE*

Research in general practice may fail to be effective if the age-and-sex composition of the practices concerned is not accurately known. Age, sex, family size, occupation, housing, and race may all affect the distribution of disease, but, of these, age and sex are so important, especially in all epidemiological research projects, that knowledge of their distribution in the practice should be regarded as a basic condition for research. This report describes a method by which a general practitioner can produce and maintain a register of this information.

In this report the word "register" is used to indicate the permanent record made. The word "census" is used to describe an age/sex breakdown extracted from the register.

The initial production of the register is somewhat laborious, but once made it can easily be kept up to date and will allow a census to be extracted rapidly at any time. For a practice of 3,000 patients with a total of 800 to 1,000 patients entering and leaving annually, maintenance of the register should take a secretary not more than two hours every month. In such a practice, an age-and-sex census could be extracted from the register in about half an hour.

It must be stressed that a register needs regular attention, and that it must be kept accurately, as all mistakes tend to be perpetuated; but if kept up to date it obviates the labour involved in preparing an age/sex breakdown of the practice population every time a research project is begun.

Making the Register

Any foolscap-sized loose-leaf method can be adapted for the purpose. Squared sheets are particularly suitable because of the ease of tabulation, but some practitioners prefer overlapping loose-leaf pages with a visible index. Both these methods are probably quicker in use than a card-index file.

1. Two separate pages are used for each possible year of birth, and the appropriate year is boldly entered in the top right-hand corner or on the visible tag. One of the pages relates to males (Fig. 1) and the other to females (Fig. 2), and one of them should bear a distinctive mark for easy recognition—for example, a flash of red ink across the right-hand top corner.

2. Lines are ruled vertically to provide columns for (a) patient's full name, (b) day and month of birth, (c) date of entry into the practice, and (d) date of departure from it. Some doctors like to have additional columns for address, N.H.S. number, etc.

3. The medical record envelopes (E.C. 5 and 6) are then worked through in sequence, and entries of the details of patients for whom the date of birth is shown are made in the appropriate birth-year pages.

4. When the year of birth is not recorded on the envelope and cannot be ascertained from consultant's letters inside, the envelope is "flagged" with a strip of card long enough to protrude conspicuously and so to bring the omission to mind.

5. A list is compiled of the names, last addresses, and N.H.S. numbers of patients whose dates of birth are missing. A copy of this list is sent to the executive council with a request for as many as possible of the missing dates. The list itself is kept in the consulting-room or the office in a place such that the practitioner and the receptionist will be reminded to collect the missing dates of birth when patients are seen. Indeed, a habit should be developed of checking the dates of

Members of the Committee: Sir Robert Platt (chairman), Dr. G. F. Abercrombie, Dr. John Fry, Dr. G. K. H. Hodgkin, Sir Wilson Jameson, Dr. B. S. Lush, Professor J. N. Morris, Professor M. L. Rosenheim, Dr. Richard Scott, Dr. G. C. Sheldon, Dr. G. I. Watson, Dr. C. A. H. Watts, and Dr. R. E. Hope-Simpson (secretary).

	Born in 1897			
	Day and Month of Birth	In	Out	
Aldridge, George	15. 5	6. 2.45		
~~Bayliss, Kenneth~~	~~2. 8~~	~~29.12.49~~	20.6.55	
Compton, David	25. 8	18. 3.50		
Godwin, Colin	26.10	16. 5.58		
~~Kemp, William John~~	~~4. 7~~	~~6. 6.55~~	3.7.59	D
Page, Frederick	10.11	30. 3.46		
Skinner, Herbert	19. 2	27. 6.52		
Taylor, Arthur	17.12	8. 9.49		
Tugwell, James	20. 6	4. 2.51		
Wallis, Harry	13. 5	6. 8.53		

Fig. 1.—A Portion of a Register of Males. The names in Figs. 1 and 2 are fictitious.

	Born in 1897			
	Day and Month of Birth	In	Out	
Abbott, Mrs. Phyllis	12.10	21. 9.51		
Butler, Jennifer Linda	9. 4	8.12.49		
Durnford, Elizabeth	29. 2	10. 1.53		
~~Edwards, Josephine~~	~~23. 5~~	~~27. 4.50~~	24.5.58	D
~~Henderson, Kathleen~~	~~31. 8~~	~~8.12.48~~	21.3.58	
Hiscock, Mrs. Doris	10. 4	18. 2.58		
Johnson, Marion	22.12	6. 3.58		
~~Rhodes, Mrs. Ethel~~	~~24. 9~~	~~9. 4.58~~	4.2.59	
Simmons, Mrs. Irene	3. 3	10. 2.59		
Tanner, Mrs. Jane	17.11	6. 6.59		

Fig. 2.—A Portion of a Register of Females.

				Date of Census: 31.12.58		
Age (Yrs.)	Yr. of Birth	Male	Female	Total	5-Year Total	10-Year Total
<1	1958	26	26	52		
1	1957	13	31	44		
2	1956	21	24	45		
3	1955	23	24	47		
4	1954	14	19	33	221	
5	1953	30	27	57		
6	1952	26	28	54		
7	1951	25	35	60		
8	1950	31	24	55		
9	1949	33	30	63	289	510

Fig. 3.—A Portion of a Census from a Register.

birth of all patients who attend, because in this way mistakes on the medical record envelopes are detected.

6. Some patients leave the district or change their addresses without notifying the executive council or the general practitioner. If there is no way of tracing them, a list of their names, males and females separately, is kept at the end of the register, and where possible the decade in which they were probably born is indicated. Whenever a census is taken the number of those persons allocated to each decade and the size of the residue for whom no reasonable guess can be made is shown.

Maintaining the Register

1. A specific time every week or month is set aside for bringing the register up to date; new entries are checked, withdrawals are recorded, and the medical records which have been recalled by the executive council are dispatched.

2. When a new patient registers with the practice the details are immediately entered into the register. The practitioner and the receptionist should develop the habit of obtaining the dates of birth of all new patients.

3. Where several surgeries are involved, temporary registers are kept at each one, and the main register is constructed from these.

4. The dates of birth are now sometimes shown on the medical cards (E.C. 4), and it is hoped that soon this will be done generally. If a medical card lacking the date of birth is sent by post or brought by someone who does not know it, an immediate request is made for it by letter.

5. Withdrawals are indicated by lightly scoring a line through the name of the patient and the dates of birth and entry into the practice, and entering the date of withdrawal in the "Out" column.

6. Deaths are recorded by entering "D" alongside the date of death in the "Out" column. The register can be used similarly to record other events of interest to the doctor, but these should not be multiplied unduly.

Extracting the Census

1. A census should be taken at least once a year, preferably on a specific date such as January 1.

2. A foolscap sheet (Fig. 3) is ruled for the following columns: age in years (0, 1, 2, 3, 4, etc.); years of birth (1958, 1957, 1956, etc.); annual number of males; annual number of females; and annual total. Subsequent columns may be used for the doctor's particular requirements—for example, five-year totals and ten-year totals.

As already mentioned, a note is made of the number in each decade whose dates of birth are unknown, and of the number of the residue for whom no guess can reasonably be made.

Some Uses of the Register

The register can be used to obtain information for many purposes. It is often of interest to compare data from a number of different practices, and, for this, age/sex breakdowns are essential.

Within a single practice it is sometimes desirable to compare the incidence of disease in different age-groups, or, in the same age-group, to compare the two sexes. For this a register is essential.

In many investigations it is important to select controls matched with cases for age and sex. This may be obtained simply and in a random manner by the use of the register.

If a census is extracted from the register and recorded at regular intervals, it is possible to work out the age incidence of diseases and epidemics several years after they have occurred. In this way the register can be used to provide retrospective information.

In partnerships it often happens that one partner only is interested in research, or that the partners have different interests. If a register is maintained, a single member of a partnership may use for detailed analysis his own cases of the disease in which he is specially interested. At the same time, if his partners co-operate by recording their cases, he will have the figures to determine the attack rate in the practice as a whole.

Most preventive medicine involves the examination of population groups of special risk. Age and sex are important in defining such population groups. If a general practitioner wishes to discover which of his patients are in a particular group—for instance, those in their first year at school—he can do so rapidly by reference to the register.

INTERNATIONAL CONGRESS OF GASTRO-ENTEROLOGY

[FROM SPECIAL CORRESPONDENTS]

An International Congress of Gastro-enterology was held in Holland during the week beginning April 19, under the presidency of Dr. A. J. CH. HAEX (Leyden). It was organized by the Netherlands Gastro-enterological Society. The scientific business consisted of five panel discussions, a large number of individual lectures, and various demonstrations. In this report we shall consider only some of the salient points which emerged from the panel discussions.

Prophylactic Shunts for Oesophageal Varices

President: O. Hoste (Belgium). *Moderator:* H. J. J. Fesevur (The Netherlands). *Panel:* J. Caroli (France), L. Demling (Germany), A. H. Hunt (Great Britain), P. Marion (France), R. Milnes Walker (Great Britain), H. Pietri (Algeria), E. Wodak (Austria).

This discussion hinged on the fact that bleeding from oesophageal varices is extremely dangerous when it occurs in the presence of cirrhosis of the liver: fatality rates of up to 50% have been recorded for the first haemorrhage. The question is then whether it is wise to perform a portal-vein shunt operation in patients with cirrhosis and oesophageal varices to prevent their bleeding. The panel was in general agreement with J. CAROLI that medical treatment with a low-salt diet, diuretics such as chlorothiazide, and corticosteroids such as prednisolone is totally ineffective in reducing portal hypertension, the size of the varices, and the liability to bleed. Did the liability to bleed from the varices parallel the degree of portal hypertension? The members of the panel were able to quote examples of heavy bleeding occurring in the absence of gross portal hypertension, but they nevertheless agreed with A. H. HUNT'S general statement that "the higher the pressure and the bigger the varices, the more likely there is to be a dangerous haemorrhage." If surgical operation was to be performed, what type of shunt should be done? Most members of the panel agreed with R. MILNES WALKER that end-to-side portacaval anastomosis was usually to be preferred. Although some enthusiasts

have advocated prophylactic portacaval anastomosis in every patient with cirrhosis, the panel thought that anastomosis should be avoided if there was evidence of gross hepatic dysfunction. Among clinical manifestations, jaundice was the most important contraindication. Among the various biochemical tests of liver function, it was generally agreed that a plasma albumin level of less than 3 g./100 ml. contra-indicated operation. The reason for caution if there is overt clinical or biochemical evidence of gross hepatic dysfunction is that the dysfunction may be aggravated by a shunt, and in particular that hepatic precoma or coma may be precipitated.

It was apparent that the panel's total experience of prophylactic shunts was not extensive, and one must conclude that the whole issue is still *sub judice*. Studies are in progress which in due course will permit a definite decision.

Crohn's Disease

President: C. Marina Fiol (Spain). *Moderator:* N. Henning (Germany). *Panel:* J. A. Bargen (United States), W. T. Cooke (Great Britain), L. Fruhlung (France), P. Hillemand (France), D. Limburg (The Netherlands), J. Massion (Belgium), R. Nissen (Switzerland).

In discussing the aetiology of regional enteritis the panel agreed that neither tuberculosis nor sarcoidosis could be implicated, though, rarely, abdominal trauma might activate pre-existing inflammatory disease. Most members had seen patients where hereditary factors could be involved, though these played a minor part. Variability in geographical incidence in parts of Europe and America was commented upon, the disease seeming only seldom to affect the negro but to develop in Jews more often than in other racial groups. The production of histologically similar bowel lesions in sensitized animals made some type of auto-immune process a possibility.

The pathological changes which distinguish this disease from tuberculosis, small-bowel tumours, and other forms of enteritis could be recognized by an experienced morbid anatomist. Clinically, regional enteritis might present in acute forms with pain in the right iliac fossa simulating appendicitis, with intermittent bouts of diarrhoea, and colicky abdominal pain with fever. Opinions differed on whether these attacks can resolve completely or whether they progress inevitably to chronic forms, and on whether appendicectomy is justifiable at this stage. In more chronic disease, bouts of diarrhoea and pain, accompanied by increasing pallor and loss of weight, were the rule; while the stools, initially watery, usually become fatty later. Symptoms and signs of a malabsorptive state were frequent. While physical examination was usually negative, tender abdominal masses, anaemia, unexplained finger-clubbing or fever, and intractable perianal disease were often found. Steatorrhoea, macrocytic anaemia, elevation of the sedimentation rate, and abnormalities in serum mucoids could usually be demonstrated. The diagnosis could sometimes be confirmed radiologically, and the way in which such changes could be distinguished from ileo-caecal tuberculosis was graphically described. Again, varying estimates as to the frequency with which these changes could be demonstrated were given, negative examination by no means excluding the disease.

The high recurrence rate after surgery had persuaded most members that initial treatment should be medical, though one member thought earlier surgery might improve the prognosis. While no specific medical treatment was available, the value of a high-protein, low-residue diet, "salazopyrin" (salicylazosulphapyridine), repeated transfusion, and steroid therapy was emphasized. J. A. BARGEN claimed that remissions had been reduced by small doses of *x* rays administered to the four abdominal quadrants in rotation. Surgery was indicated only if complications such as fistulae, obstruction, severe perianal disease, perforation, or bowel haemorrhage made it necessary. The relative merits of excision and exclusion procedures were discussed. It seemed that all the surgeons present favoured excision, though there was no objective proof that this caused reduced recurrence rates. The risk of blind-loop syndromes was reduced by the employment of end-to-end anastomoses, and pleas were made for surgery to be as conservative as possible lest post-resectional nutritional problems arose. There was general agreement that recurrences after operation developed in between one-third and two-thirds of the patients treated and that most patients would eventually require operation. Recourse to surgery, however, did not necessarily adversely affect the long-term prognosis.

Despite this vigorous and interesting discussion, few problems concerning this controversial disease seemed to have been solved.

Hepatic Coma

President: H. Kapp (Switzerland). *Moderator:* H. Schrijver (The Netherlands). *Panel:* W. V. McDermott (United States), T. Kitani (Japan), G. A. Martini (Germany), G. Schouwink (The Netherlands), S. Sherlock (Great Britain), J. Vandenbroucke (Belgium), A. Varay (France), J. M. Walshe (Great Britain), F. Wewalka (Austria).

During recent years much attention has been given to the neuropsychiatric manifestations of liver disease. These occur in two main groups of patient—namely, those with acute hepatic failure (e.g., because of a fulminant infective hepatitis) and those with cirrhosis of the liver associated with an extensive portal collateral circulation (sometimes man-made in the form of a portacaval anastomosis). G. SCHOUWINK described the variable symptomatology, which may mimic hysteria or Parkinsonism or may include depression, excitement, or altered personality. Some patients suffer from hallucinations or attacks of loss of consciousness. During the stage of hepatic precoma a "flapping tremor" of the outstretched hands can commonly be elicited. Deep coma may also occur. J. VANDENBROUCKE discussed some of the tests available for the recognition of hepatic precoma and coma. There are no truly specific lesions of the liver as the underlying cause. Abnormal liver-function tests are of great value in making the diagnosis, but are not closely correlated with the development of coma. Clinical judgment is superior to both histological and biochemical tests in prognosis. The electroencephalogram is usually abnormal, with the so-called "coma pattern," but this change is not specific to hepatic coma. Nevertheless, T. KITANI regarded the E.E.G. as valuable in judging the prognosis in hepatic coma and precoma, stating that when the record is a flat one and remains so in spite of treatment the prognosis is poor even if the patient temporarily shows clinical improvement.

So far as treatment is concerned, the panel members were in general agreement that a diet containing very little protein, and sterilization of the gut by antibiotics, such as neomycin, to reduce absorption of nitrogenous material, are of great importance. For chronic cases a low-protein diet and sterilization should be persisted with. In actual coma, other methods are available. Haemodialysis had been used by some members of the panel, but it was often not effective even when nitrogenous levels of the blood were reduced and the *p*H was brought to normal levels. Salts of glutamic acid are probably valuable, and they act chiefly, according to J. M. WALSHE, by binding ammonia in the tissues. He stated that there were no theoretical reasons why arginine and ornithine should be valuable, and the other members of the panel were unable to give convincing practical evidence of their benefits. According to G. A. MARTINI, corticosteroid treatment should be used if the coma is due to an active inflammatory lesion of the liver, but it is useless in the "secondary" type of coma of chronic liver disease, while F. WEWALKA went further and stated that corticosteroids could actually provoke coma in chronic liver disease.

Treatment of Ulcerative Colitis

Moderator: S. C. Truelove (Great Britain). *Panel:* S. Aylett (Great Britain), H. E. Bacon (United States), R. Cattan (France),

M. Demole (Switzerland), J. J. Groen (Israel), J. F. Pontes (Brazil), N. Svartz (Sweden), G. Watkinson (Great Britain).

At the present time opinions diverge markedly on the value of different methods of treating ulcerative colitis. N. SVARTZ described the use of salazopyrin, of which she was the originator and which is generally accepted as a valuable form of treatment. G. WATKINSON agreed that salazopyrin was frequently beneficial, but he dealt chiefly with the results of corticosteroid treatment, both systemic and local. He reviewed the controlled therapeutic trials which have demonstrated the usefulness of corticosteroid treatment, both by systemic and by local routes of application.

Surgery is sometimes necessary in the acute attack if the illness resists medical treatment or if a dangerous complication develops requiring surgery; and elective surgery is necessary in some patients with chronic disease. H. E. BACON advocated total colectomy with permanent ileostomy as the usual surgical procedure, but S. AYLETT considered that a majority of the patients coming to radical surgery could be treated satisfactorily by colectomy and ileo-rectal anastomosis and so avoid an ileostomy life. J. J. GROEN made an eloquent plea for psychotherapy as the basis of treatment, although agreeing that one would be cautious about its use in severely ill patients at the height of a bad attack. It was conspicuous that he favoured superficial psychotherapy administered by the general physician or gastro-enterologist rather than formal deep psycho-analysis carried out by a professional psychiatrist. R. CATTAN struck a new note by recommending the use of prefrontal leucotomy by electrocoagulation as a treatment for severe ulcerative colitis, asserting that it was especially beneficial in checking haemorrhage from the bowel. The other members of the panel were somewhat sceptical of the value of this treatment, chiefly because Cattan had had several deaths in a comparatively small group of patients thus treated.

Carcinoma of the colon is much more apt to occur in sufferers from ulcerative colitis than in the general population. The physicians on the panel thought that the risk was comparatively low, being less than 5% in their experience. However, the surgeons, who based their results on actual operation specimens, considered the risk to be of the order of 25% in patients with the disease for more than 10 years. The true incidence is likely to be somewhere between these two estimates. However, no member of the panel advocated colectomy in every patient with ulcerative colitis purely in order to eliminate the risk of subsequent carcinoma. All agreed that the patients, even though symptomatically well, should be under regular medical supervision and should have annual or biennial barium enema investigations in the hope of detecting carcinomatous change early if it should occur.

This discussion demonstrated that advances in treatment, both medical and surgical, are occurring in this disease, but that there is still lacking that precise knowledge of aetiology without which medical treatment must continue to develop along empirical lines.

Hepatitis and its Treatment

President: G. Sotgiu (Italy). *Moderator:* L. Schalm (The Netherlands). *Panel:* M. Bjørneboe (Denmark), W. J. Bruins Slot (The Netherlands), T. C. Chalmers (United States), R. Crismer (Belgium), H. Kalk (Germany), H. G. Mogena (Spain), H. Staub (Switzerland), W. J. H. Summerskill (United States).

It has long been an accepted part of the therapy of acute hepatitis that bed-rest should be enforced, but the careful controlled studies of T. C. CHALMERS and his colleagues showed that this might not be necessary. Over a hundred Service men with hepatitis kept at strict rest fared no better in duration of hospitalization and incidence of relapses and re-hospitalization than did a similar number who were allowed up early. Early ambulation was said to reduce appreciably the incidence of residual neurosis. The epidemic from which these patients were drawn was shown to be of comparable severity to others investigated, but it was admitted that no data were available on the effect of early ambulation on older or on female subjects. Most of the European members still favoured bed-rest, though they admitted they had few data to support their contention. It seemed that increased activities might be permitted in young adults, but that bed-rest should be enforced in the middle-aged and the elderly and if pregnancy complicated the condition. It was felt that a high-calorie diet with a low-fat content should be given, there being some evidence that early intake of fat predisposed to fatty change in the liver. It was also generally agreed that alcohol should be withheld during, and for a period after, an attack, but T. C. CHALMERS again emphasized that unnecessary restrictions would predispose to neurosis. Steroids were recommended in the severe protracted case, in the early case in which coma, ascites, or oedema had developed, and in the elderly, in whom the prognosis had been shown to be appreciably worse. They seemed to reduce anorexia, thus enabling a more liberal diet to be taken, and might be of some value in differential diagnosis from an obstructive jaundice. Some panel members used prednisone routinely, regardless of age or severity, but further controlled trials must be undertaken before this course could be recommended.

On criteria of cure a considerable difference of opinion emerged, some members believing it was possible on clinical grounds alone, others favouring serial liver-function tests, while yet others felt that repeated liver biopsies should be undertaken. Probably serial estimations of serum bilirubin and transaminase levels were to be preferred. Interesting information about the patchy involvement of the liver in hepatitis, obtained by laparoscopy, underlined the limited value of needle biopsy.

In the discussion on subacute or chronic hepatitis the difficulties in diagnosing and defining the condition were emphasized; it might be simulated by granulomata, sarcoidosis, and toxoplasmosis. Here it was felt that bed-rest should be enforced, but few other measures had been found of value. Steroids had been shown to exert a favourable influence by M. BJØRNBOE, who found that only 35% of untreated patients survived two years, as compared with 75% who had received steroids. The treatment seemed of most value in post-hepatitic cases and of little value where alcoholism had been the cause. A plea was made for a properly controlled trial: and the rarity of the condition makes it desirable that this should be on a national scale. The value of this type of investigation was shown in studies made of the outcome of hepatitis in the British Army, where the appreciably worse prognosis of serum hepatitis had been clearly demonstrated.

It seemed that a firm case has been made for earlier ambulation in this disease. Rest, diet, and steroid therapy hasten recovery in severe protracted disease. Further controlled trials, on the lines being followed by T. C. CHALMERS, seem vital to investigate the problem further.

ROYAL SOCIETY OF HEALTH

ELIMINATION OF TUBERCULOSIS

Nearly 3,300 delegates attended the Congress of the Royal Society of Health in Torquay last month and heard Lord MORRISON OF LAMBETH say in his presidential address that he had become increasingly apprehensive about hospital administration, and that there should be a substantial transfer of hospital services back to local authorities.

There were 12 sectional meetings, ranging from executive council services to world health and tropical hygiene, during the Congress, and five conferences, including that of the Medical Officers of Health reported below.

M.O.H.'s Conference

The presidential address to the Conference of Medical Officers of Health was given by Dr. J. STEVENSON LOGAN, and ranged over sociological research, community mental health, and health education. In the field of sociological

research, he suggested, we must follow the same principle of asking "What happens and why?" which had led to progress in medicine, instead of arguing endlessly about what should ideally occur.

Exit Pulmonary Tuberculosis

A symposium on "Pulmonary Tuberculosis—the Last Stages?" followed the presidential address.

Dr. V. H. SPRINGETT (medical director, Birmingham Chest Services) said that experience in Birmingham had confirmed Crofton's finding that co-operative patients with organisms sensitive to at least two of the three main drugs could be made sputum-negative in less than a year without surgery; such patients should be treated in hospital both from the point of view of controlling infection and of ensuring that they received the drugs. As to the future, Dr. Springett considered that tuberculosis might be eliminated in Britain in 25 years. Estimates of 5 to 10 years for the disappearance of this disease were unduly optimistic; even if eliminated as a cause of death, tuberculosis would remain a serious public-health problem for the next few years.

Professor A. B. SEMPLE (professor of public health, Liverpool University), dealing with the role of the local health authority, urged other authorities to use, as Liverpool had done, the power of compulsory removal to and detention in hospitals given by s.172 of the Public Health Act, 1936, of persons suffering from infectious tuberculosis who could not be persuaded to have treatment. He briefly described the Liverpool mass radiography campaign of February and March, 1959, and said that one interesting aspect of the 1,045 cases of active disease found was the number of cases previously known whose lesions on radiographic examination showed signs of renewed activity after they had been removed from the register.

Dr. T. M. POLLOCK (Medical Research Council, Tuberculosis Research Unit) said that the undoubted protection conferred by B.C.G. on young adults had been shown to last for at least seven and a half years, and its contribution to controlling the disease increased with each year of protection. It was significant that the M.R.C. trials had shown that about one-fifth of 13-year-olds in Great Britain were tuberculin-positive and that this group was contributing substantially to the notifications of tuberculosis during adolescence and early adult life. Little more than one-third of 13-year-old children were currently receiving B.C.G. vaccination. Of the unvaccinated two-thirds, one-fifth were tuberculin-positive and ineligible, but the remainder were not being protected either because their parents refused or because there was no L.H.A. scheme. Objections to B.C.G. on account of safety or efficacy were not supported by the clinical trials or by experience.

Tuberculosis in a Group Practice

Dr. E. V. KUENSSBERG (general practitioner, Edinburgh) gave an interesting and perhaps surprising account of the extent of tuberculous illness still encountered in a group practice in a semi-industrial estate. Although new cases had dropped from 7.64 per 1,000 patients in 1951 to 1.01 in 1959, there were still 37.81 old cases per 1,000 patients in the latter year. He spoke of the much higher yield from "doctor's referrals" in his group than from the mass radiography surveys. Detection of cases was greatly aided by close collaboration with health visitors, whom they met weekly. Co-operation with the public-health department and chest clinic in their area, though good, was not perfect, as was illustrated by the fact that out of 40 new cases picked up by the Edinburgh mass survey in 1954 more than half had been on the local authority's register unknown to the general practitioner concerned.

The discussion was opened by Dr. H. R. EDWARDS (Yale University and New Haven Medical Center), who felt that the British use of B.C.G. was at present more enterprising than that in America. He thought 25 years might be an underestimate of the time required to banish tuberculosis.

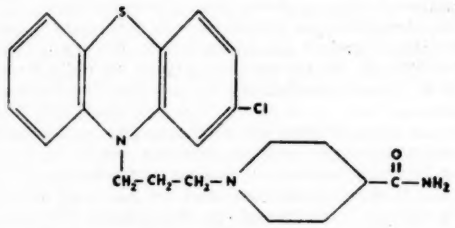
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Pipamazine

"Mornidine" (G. D. Searle).

Chemistry.—This is 10-[3-(4-carbamoylpiperidino) propyl]-2-chlorophenothiazine, and has the following structural formula:



Pharmacology.—Pipamazine belongs to the phenothiazine group, a class exerting two principal effects—subcortical sedation resulting in tranquillization, and a specific inhibitory action on the vomiting centre. Pipamazine is said to cause little tranquillization at normal dosage levels, while extrapyramidal side-effects have been reported only on overdosage. Against apomorphine-induced vomiting in dogs pipamazine was approximately 25 times as effective as chlorpromazine—a potency comparable to perphenazine. The drug causes less depression of the central nervous system in dogs and less potentiation of barbiturate in mice than does chlorpromazine.

Hypotensive side-effects are theoretically possible; pipamazine blocks and may reverse the pressor effects of adrenaline and some other pressor drugs, but noradrenaline and phenylephrine are still effective. Acute toxicity studies on rats indicate a high therapeutic ratio. Chronic toxicity has been studied in rats and dogs without revealing harmful effects.

Therapy.—Pipamazine has been used successfully in the treatment of nausea and vomiting of pregnancy, the usual oral dose being 10 mg. at bedtime, 5 mg. on waking, and a further 5 mg. later in the day if necessary. In other conditions one 5-mg. tablet every 4–6 hours is suggested. In such conditions the use of the oral route may limit efficacy; there are reports of parenteral administration abroad, but we understand the drug is available only as tablets in Great Britain at present. Reports indicate that pipamazine (intramuscular) is effective in decreasing the incidence of post-operative vomiting and also in combating nausea accompanying radiation therapy. In some chronic schizophrenics large doses (30–600 mg. daily) produced orthostatic hypotension and signs of extrapyramidal disturbance.

Contraindications.—Pipamazine should not be given to patients with depression of haemopoietic function. Caution is necessary when it is given with other depressants of the central nervous system or when there is a tendency to hypotension (e.g., injury, anaesthesia). The potent antiemetic effect may obscure diagnosis in organic vomiting from intestinal obstruction, brain tumour, etc.

Toxicity.—Possible side-effects include hypotension, extrapyramidal dysfunction, and depression of bone marrow. Serious liver damage has not been reported. Two cases of accidental poisoning in small children produced pupillary constriction and heavy sedation, but the patients recovered.

N.H.S. Basic Price.—100 5-mg. tabs. for 20s. 6d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Masks or Silence

SIR,—I am dismayed by your leading article (April 30, p. 1339), which by title, content, and conclusion seems to condone dirty surgery. Why masks *or* silence? Why not both—the best masks we can devise and the degree of silence that is compatible with all a surgeon's duties, including teaching as well as operating?

You say of pathogenic organisms in the nasopharynx —*Streptococcus pyogenes* and *Staphylococcus aureus*— that "it has not in fact been shown that these two pathogens are expelled in large numbers." Are not small numbers enough to infect a wound? You say that when a carrier of these pathogens is put into the same position as a surgeon while performing an operation and talks for five minutes "he may fail to project this organism"; but supposing he does not fail, will the wound not be infected? You say that "even when this organism did appear on the culture plates not more than one or two colonies were obtained." How many colonies do you want to infect a knee-joint? After quoting these researches of twenty to forty years ago you refer to one recent study by Shooter and his colleagues, who found that "when 21 known carriers of *Staph. aureus* talked for fifteen minutes in this apparatus only three colonies of this organism were obtained." That was enough to wreck the lives of three patients by ankylosis of a joint. Does it not matter that it was only three?

Having first said that "*Staph. aureus* is found so infrequently in the mouth that its expulsion in droplets of saliva is improbable," you go on one column later to quote Shooter's observations on *Staph. aureus*: "of 53 masks after use for some time in the theatre . . . no fewer than 33 were contaminated on the inside and 21 on the outside." As if this contradiction was not enough you conclude that a surgeon not unusually puts his mask in his pocket (as if theatre dress had any pockets) and thus contaminates himself with his own organisms so that it would have been better "if he had not been provided with a mask." You might just as reasonably say that surgeons who put their gloves in their pockets and then use them for another operation would be better without gloves. Of course they would; but which clean surgeon does either of these dirty things?

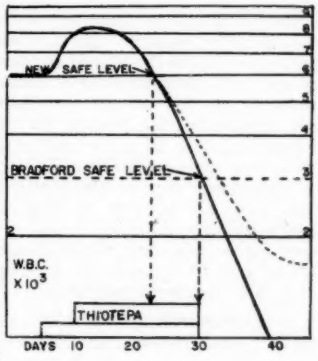
You have stirred me into writing because this is just another niggling attempt to undermine what you care to call "the ritual of an operating theatre," but should have been called the first principles of asepsis. We have already had enough, especially, of course, when penicillin first became available, and in consequence have bred untold millions of insensitive pathogens. If any surgeon tells me that he has never yet had unexpected infection of an elective operation wound I will listen to him. If any research worker tells me of another precaution I can add to those already in use—as, for example, the double sterile masks, one closely fitting round the nose, mouth, and side of the face with a second "opaque" mask on top, each changed regularly, which we have used at the London Hospital for twenty years but apparently was not studied by any of your experimenters—I will listen to him. But if you tell me not to bother about masks, or gloves, or proper scrubbing-up, or non-touch technique, or any other detail, because nothing much will happen very often and there will be few disasters, I will listen not to you but to the few victims of the disasters.—I am, etc.,

London, W.1. REGINALD WATSON-JONES.

"Bradford Approach" to Breast Cancer

SIR,—In May, 1959, a stir was caused in both medical and lay press with the publication of the article "Breast Cancer: A New Approach to Therapy" by Mr. G. Whyte Watson and Dr. R. L. Turner (May 23, 1959, p. 1315). During August and September their method was given a trial in this hospital.

Eleven patients with advanced and metastatic breast cancer were treated exactly as advocated in the publication. Within one month seven patients had died, and in our opinion death was hastened by an irreversible pancytopenia directly attributable to the treatment given. Of the remainder, one has been lost to follow-up, one suffered a reversible pancytopenia, but has shown a striking remission for six months, and the remaining two have had partial remissions lasting two and four months respectively. Analysis of the haematological findings reveals a constant pattern, upon which we believe far more reliance can be placed than accepting an arbitrary "safe level" of 3,000 W.B.C./c.mm. When the serial white counts are plotted semi-logarithmically a useful graph is obtained, which shows a striking rise during the initial testosterone therapy, and a precipitous fall, often to fatal limits, if the thio-TEPA is continued until the white count falls to 3,000.



Our experience subsequently has confirmed our initial impression, that the "safe level" at which the thio-TEPA therapy should be stopped corresponds to the pre-treatment white-count figures as indicated in the above Graph. It is important to have a number of blood counts to establish a baseline before starting the testosterone therapy and a sufficient number subsequently to even out the various errors inherent in white-cell counting. With the safeguards mentioned above we believe that this method may have a useful place in the management of breast cancer, but would hesitate to advocate it in preference to presently accepted methods.—I am, etc.,

W. D. RIDER,
for the Clinical Investigation Committee,
The Princess Margaret Hospital and
Ontario Cancer Institute.

Toronto, Canada.

Ischaemia in Limb Injuries

SIR,—We thank Mr. S. Mottershead for his comments (April 30, p. 1361) on our article (April 2, p. 1001), and have noted his criticisms. We agree that most of the cases we tackled were very unfavourable, but cannot entirely accept his strictures for making the attempt to

salvage limbs which were otherwise certain, we assure him, to be lost. He asks, what did we expect, and why were we disappointed ?

In the circumstances we did not expect more than we achieved—namely, four good limbs from eleven cases of severe traumatic ischaemia. We were disappointed, not with the results of arterial reconstruction, but with the fact that prevailing views on limb ischaemia led to the referral of cases far too late. Arterial reconstruction is a relatively new technique, and information on its applicability to limb injuries is still needed. Moreover, our favourable experience with improved techniques in late embolectomy[1] encouraged us to see if the same results could be obtained in long-standing ischaemia due to arterial injury; our findings suggest that, because of damage to collaterals, the ischaemia of injury is likely to be more complete than in embolism and that infection of the ischaemic tissue from the open wound may well play an important part; the attempt at reopening the artery must therefore be made early before necrosis can occur. The parallel which Mr. Mottershead seeks to draw between traumatic ischaemia and cold injuries such as frostbite has no physiological justification, and we are surprised that he should make it.

We are unable to share Mr. Mottershead's belief that, as the result of spasm, "the superficial femoral artery can contract down to the size of the lead in a pencil," unless, of course, he is referring to a 6B pencil. The substance of the walls of an artery can scarcely disappear in this way. What *can* happen is that trauma may disrupt the medial and intimal coats of an artery and leave the ends united by an intact but attenuated sleeve of adventitia. This can give an appearance such as Mr. Mottershead describes, and thus may arise an example of that "imprecise observation" which we have criticized in our article. We would repeat that we do not deny the existence of arterial spasm, but would seek to diminish the emphasis hitherto placed upon its role in traumatic ischaemia.

Mr. Mottershead concludes by asking us to remember that "authoritative writings are authoritative." We are not quite sure how he intends this to be interpreted. Does he mean that the teachings of the great should never be challenged ? If this were so, it would be a poor outlook for medical progress.—We are, etc.,

Chester Royal Infirmary, Chester. E. G. HARDY.
Royal Victoria Infirmary, Newcastle upon Tyne. D. J. TIBBS.

REFERENCE

[1] Tibbs, D. J., *Postgrad. med. J.*, 1960, **36**, 283.

SIR,—Although we have seen the condition of colliquative necrosis sporadically from time to time, we feel this abridged case report is worthy of record, particularly after Mr. E. G. Hardy and Mr. D. J. Tibbs's excellent description in their article on acute ischaemia in limb injuries (April 2, p. 1001).

F. L., a 58-year-old man, was admitted to hospital with a sudden onset of severe pain in his right calf. He also stated that he was unable to use the limb. Examination showed a pale, cold leg with a palpable popliteal pulse but no distal pulses. A diagnosis of embolus was made and the popliteal artery was explored some five hours after the onset of the pain. There was a thrombosed aneurysm of the popliteal artery with a good pulsation immediately proximal. The vessel beyond the aneurysm was of good calibre, but there was no backflow of blood. The posterior tibial artery was then exposed behind the medial malleolus and retrograde flushing produced a length of embolus. A bypass graft was inserted from above the aneurysm to immediately below it. The operation was completed seven hours after the acute episode, and the circulation to the foot was much improved.

However, a gross oedema of the leg was noted 12 hours later and a fasciotomy was performed; the graft was found to be patent. The foot became gangrenous and a below-knee amputation was performed one week later. All the muscles were divided at the level of amputation; again the graft was found to be patent. This was followed by an aseptic colliquative necrosis of the amputation stump. Disarticulation at the knee-joint and debridement were performed. Only the muscles of the posterior compartment were found to be affected; the muscles of the anterior compartment and also the skin were quite healthy. Thereafter the amputation stump improved rapidly.

It is interesting that, as Mr. Hardy and Mr. Tibbs noted, despite adequate blood supply, the necrotic process continued at a rapid rate. It is also obvious that, in this case, the whole muscle group should have been excised, and not simply divided at the time of the original amputation—in this patient it would have avoided a further unnecessary operation.—We are, etc.,

P. MARTIN.
J. RUDICK.
B. R. MEYEROWITZ.

Hammersmith Hospital and Postgraduate Medical School, London, W.12.

Is Trichomonal Infestation Venereal ?

SIR,—In 1957, with the co-operation of the consultant gynaecological staff of St. Mary's Hospital for Women, Manchester, and in association with Dr. R. F. Jennison, I investigated 30 male patients whose wives were being treated for vaginitis due to *Trichomonas vaginalis*. In addition to clinical examination, specimens were obtained from the sub-preputial sac, urethra, prostate, and urine of each patient and subjected to direct microscopy and culture. Eighteen (60%) showed cultural evidence of infection with *T. vaginalis*. In a control group of 50 unselected, presumably promiscuous, male patients attending a venereal-disease clinic, 4 (8%) showed evidence of infection with *T. vaginalis*. This investigation, which was unpublished, would appear to confirm the growing belief that at least in such a highly selected group *T. vaginalis* may be transmitted during sexual intercourse.

One side-issue apparent in the study group, who were all seen in a gynaecological out-patient department not in any way connected with a venereal-disease clinic, was the attitude towards investigation. All the husbands requested to come for investigation did so, but practically everyone queried the possibility of venereal disease, and, in spite of repeated reassurance and explanation, some still harboured lingering doubts as to the nature of the infection. It was difficult to make it clear that there were certain infections of the sexual organs possibly transmitted during sexual intercourse which did not necessarily involve infidelity on either their part or the part of their spouses.

In the lay mind, venereal disease represents not so much a disease associated with sexual intercourse as such, but a condition associated with promiscuity, and a moral and social disaster rather than an infection. As a venereologist I would therefore disagree with Dr. R. D. Catterall and Dr. C. S. Nicol (April 16, p. 1177) when they suggest that, because this infection may be transmitted during sexual intercourse, patients should be referred to a venereal-disease clinic. The stigma attached to venereal-disease clinics and to patients attending there is undoubtedly nowadays less than previously, but nevertheless it exists. Until the words "venereal disease" lose the implications which they have for the majority of the lay public, to be referred to a known venereal-disease clinic for investigation of a *T. vaginalis* infection will cause many grave anxiety and in some instances may raise doubts as to the fidelity of the opposite partner. There is no suggestion as yet that promiscuity is in any way involved in the acquisition of *T. vaginalis*, and

it is common knowledge that it occurs in elderly matrons and on occasion in virgins whose chastity would appear to be beyond doubt.

For this reason—and surely the patient's peace of mind is an important reason—if the partners of patients suffering from *T. vaginalis* infections are to be investigated, then this examination, at least in the present state of our knowledge, should take place in some department other than the venereal-disease department. Only a proportion of *T. vaginalis* infections is uncovered in venereal-disease clinics; many more come to light in departments of gynaecology. It would seem reasonable, therefore, to conduct the examination of partners in association with that department. By all means let the venereologist carry out the examination of contacts, especially males—who better qualified?—but not in his venereal-disease clinic.—I am, etc.,

St. Luke's Clinic, Manchester, 3. LESLIE WATT.

SIR,—Is trichomonal infection a venereal infection? Like monilial vulvo-vaginitis, no doubt it can be, but that surely is no reason for practitioners to send their patients with an undiagnosed vaginal discharge directly to the department of venereology, as advised by Dr. R. D. Catterall and Dr. C. S. Nicol (April 16, p. 1177). A consultant either at his rooms or in a properly equipped and staffed gynaecological out-patient clinic should surely first be consulted. Moreover, this does not preclude a study of the husband, especially if there is a relapse in his wife's vaginitis after treatment. A suitable time and place is, of course, obligatory for private consultation, perhaps at times when male fertility problems are under study.

My colleagues and I in departments of gynaecology would concede that the 12 worried concubines from London and Leeds mentioned in the report were correctly passed straight through to the V.D. department. But surely, if the family doctor feels that his patient requires investigation and treatment which he cannot undertake, the great majority of ordinary patients need only visit a suitable department of gynaecology, or, if pregnant, an antenatal department.—I am, etc.,

H. C. MCLAREN.

Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Birmingham, 15.

Spiritual Healing

SIR,—There are some observations in your leading article (May 7, p. 1417) concerning the permissions granted by hospital authorities to members of the National Federation of Spiritual Healers to attend the sick in hospitals at the patient's request and with medical consent, also some personal references to myself, that need an answer and some explanation.

The imputation is that the Federation can "congratulate" itself on "slipping through the guard" of the hospital authorities by misrepresenting the attitude of the British Medical Association. This is not true. I wrote to the Association on October 13, 1959, explaining our intentions, and in return I received an encouraging reply with no hint of disapproval, and which actually contained helpful advice upon procedure. Further, hospital authorities have been writing to the B.M.A. for guidance, and the subject has received continuous press publicity. That the Association has allowed seven months to pass before formally considering the matter is purely its own concern, but to now suggest that we have been guilty of slyness and misrepresentation is unworthy.

The published criticisms have so far been undefined; the only pertinent one is that mentioned in your leading article, that when our members attend patients "they are not entering hospitals to give spiritual or religious help but to treat disease." I would wish to make it plain that our members attend patients for both purposes—i.e., to give spiritual guidance, to maintain morale and treatment to cure disease. Your leading article acknowledges the belief of healers that they can cure disease, and in this respect I would remind your readers that the Association has declared on more than one occasion that through spiritual healing recoveries have taken place which cannot be accounted for by medical science. As this is so, then why deny a patient the benefit of this, if he requests it?

You express the hope that questions will be asked in Parliament. Then why not do it, instead of hoping for it? We shall welcome the reaffirmation in Parliament that the attendance of a healer is one to be decided between the patient and the doctor. The only way the Association can intervene is by instructing its members to withhold consent for a healer to attend his patient. If it should do this the repercussions will be unfortunate, creating a hostile public opinion and disquiet.

Other comments in your leading article are concerned with questioning the efficacy of spiritual healing, and I would value a little space to refer to them. Before doing so, I would say that the granting of permissions does not imply acceptance, directly or indirectly, by the medical profession of the efficacy of spiritual healing. You state that the evidence I have given in favour of spiritual healing "would not satisfy anyone with a scientific training." Elsewhere you suggest that healers are led to wrong conclusions concerning their cures, because the patients' diseases had been wrongly diagnosed, or the recovery was due to a "remission, spontaneous healing, or suggestion."

I venture to express the opinion that so far no bona-fide investigation by scientifically trained medical men into spiritual-healing successes has ever taken place. The only occasion within my knowledge when this was attempted was the occasion when the Association appointed a special committee to investigate the evidence for healings that I submitted to the Archbishops' Commission. I questioned the committee's findings, for the reasons that it did not interview any one of the patients, that it did not call for any medical history, nor did it ask for any hospital or other medical records, *x*-ray plates, etc. In one exceptional case of full recovery from undiagnosed incurability no investigation took place, for the reason that, the patient being so well, he had not a local doctor—although the medical records were available at Great Ormond Street Hospital.

The terms "mistaken diagnoses and prognoses, remissions, spontaneous healings, etc." have provided the escape routes in the past to evade recognition of spiritual-healing successes. The most common evasion is that the doctors must have made a wrong diagnosis, for if the patient recovers he could never have had the disease. This pays a poor compliment to medical competency when so much of our evidence is dismissed on this pretext.

We wish for co-operation between medical practice and spiritual healing. We believe they are complementary to each other. I confidently anticipate this will be proven as time goes on, through the attendance of our members on patients in hospitals, when it will be seen that speedier recoveries take place than could be medically anticipated. We shall be compiling records of such cases; indeed, this has already commenced.

Finally, may I express through your columns the Federation's thanks and appreciation for the kindly

welcome that has been extended by the medical staffs to all our members who have already attended patients under this scheme ?—I am, etc.,

HARRY EDWARDS,
President, National Federation of Spiritual Healers.

Shere, Surrey.

Laissez-faire Antenatal Care

SIR,—Three new patients have recently moved to this area and joined our antenatal clinic. They were all about 28 weeks pregnant on arrival. They had each been seen once by their previous doctors, but had not had blood tests or iron tablets. One, who had repeatedly asked for a prescription, had been told "that he (the doctor) did not believe in iron tablets." Admittedly antenatal care is a long and tedious business and it is difficult not to be a little unenthusiastic about a patient who is leaving one's practice area. But even if one has decided to allow the receiving doctor to cope with the whole pregnancy, what can possibly be the objection to a rapid prescription for 100 ferrous sulphate tablets once a month ? The cost is negligible, the side-effects usually few, and the time taken to write the prescription a matter of seconds. My three patients had haemoglobins of 64%, 68%, and 80% ; in other words, two out of three were seriously anaemic.

Is there still a school of laissez-faire antenatalists in the matter of anaemia of pregnancy, and if so would somebody please explain to me their reasoning ?—I am, etc.,

HAMISH NICOL.

Lewes, Sussex.

Wards for Non-smokers

SIR,—Dr. David A. Herd's letter (April 23, p. 1276) recalls the remarks of Sir William Osler himself, who suffered personally in the same way and yet, in this one matter, failed to impress his generation with his teaching. The truth surely is that doctors who smoke become laymen for this purpose, and have a blind spot for their own addiction. Tobacco has become indispensable to them, and so it ought to be at least harmless to everyone else. Tobacco-sensitivity, if it exists at all, is the plea of the crank or the social misfit.

So far as hospitals are concerned, Dr. David Herd need not confine his comment to the wards. Early this year I received a questionary from our leading chest hospital in London inquiring after a young woman who had failed to keep up her attendances in the out-patient department. It fell to me to have to reply that, despite notices posted in the department forbidding smoking, the consulting physician himself chain-smoked whilst examining her, with the result that she had the greatest difficulty in getting home after each attendance. —I am, etc.,

JOHN DANCY.

Richmond, Surrey.

Addiction to Hypnotics

SIR,—In your annotation "Report on Addiction" (January 23, p. 260), being a digest of the *Interim Report of the Interdepartmental Committee on Drug Addiction* (1960, H.M.S.O.), your writer reports the conclusion that cases of habituation to the two mild hypnotic drugs carbromal and bromvaletone were found to have been "numerically very few, but individually serious." Whilst this may be so in England, there is reason to believe that it is not universally true. Indeed, much habituation to both unrestricted and restricted drugs is undisclosed and unrecognized. In Australia habituation to carbromal and bromvaletone is far from infrequent. It may well be that in England, under the conditions of the National Health Service, other more potent sedatives (e.g., barbiturates) are more easily and cheaply available (especially as such patients often obtain supplies from two or more medical sources concurrently) so that bromoureide habituation is less prevalent at the expense of barbiturate habituation.

Routine screening of female admissions to an acute psychiatric hospital in Victoria disclosed, in the space of two months, no fewer than 15 cases (about 5% of admissions) with markedly raised serum bromide levels—in seven instances over 100 mg./100 ml. In all but one patient this had resulted from taking unprescribed carbromal/bromvaletone-containing preparations (6 to 30 tablets per day), usually over prolonged periods, although many denied or grossly underestimated their consumption until confronted with the blood findings. Bromism, bromide psychosis, or marked withdrawal symptoms occurred frequently. In an acute psychiatric unit in Western Australia dealing mainly with patients with neurosis or personality disorder an even higher prevalence of bromoureide habituation has been noted.

A clinical and psychometric study of consecutive admissions showing raised serum bromide levels to an acute psychiatric "receiving house" is in progress and will, it is hoped, be published in due course. Preliminary impressions suggest that the vast majority of these patients are not representative of the psychiatric population at large but are essentially of neurotic drug-dependent personality, and most were currently or previously habituated to analgesics, alcohol, barbiturates, etc., in addition to carbromal.

In view of the many recent comments on the unrestricted sale of carbromal/bromvaletone preparations one aspect should be borne in mind. If, in fact, carbromal habituation is largely confined to a selected group of neurotic individuals of potentially drug-dependent personality, restriction of its sale may do little for the basic problems other than to induce some to satisfy their dependence elsewhere. Although cases of drug habituation are "individually serious"—the seriousness from a prognostic point of view stems more from the patient's personality defect than from the particular drug of habituation.—I am, etc.,

I. PIERCE JAMES.

Heathcote,
Perth, Western Australia.

Therapeutic Abortion

SIR,—Drs. M. I. Drury and M. K. O'Driscoll (March 26, p. 964) state that "the hazards of termination of pregnancy, even in healthy women, are well established." In Sweden 22,933 legal abortions were performed between 1949 and 1953 with 9 deaths, a rate of 0.4 per 1,000 operations. In 1952–3 only two deaths occurred in connexion with legal abortion, a rate of 0.2 per 1,000.[1] A medically qualified abortionist in America has published a series of 5,210 abortions with only 2 deaths.[1] I hope that people who "cannot claim exception from personal conviction" will allow that a mortality of less than 0.04% is good for any operative procedure.

We are told that in a series of 539 cases of rheumatic heart disease in pregnancy it was not considered necessary to terminate any of these pregnancies. Study of the original papers reveals that in the first series of 175 patients[2] 11 of these were dead within the next three years. As five of the deaths occurred twelve months after confinement they chose to ignore them for statistical purposes. In the second series of "289 further cases"[3] we are not told the actual number of patients involved, nor are we told anything about their subsequent fate except that "one mother did not survive

the puerperium." The paper by Sutherland *et al.*[4] concerned 252 patients with cardiac lesions in pregnancy, of whom 6 died during or soon after their confinements. —I am, etc.,

London, S.W.11. PETER DARBY.

REFERENCES

1 *Abortion in the U.S.A.: A Conference Sponsored by the Planned Parenthood Federation of America Inc.*, ed. by M. S. Calderone, 1958. Hoeber-Harper, New York.
2 Drury, M. I., O'Driscoll, M. K., Hanratty, T. D., and Barry, A. P., *Brit. med. J.*, 1954, **1**, 70.
3 O'Driscoll, M. K., Barry, A. P., and Drury, M. I., ibid., 1957, **2**, 1090.
4 Sutherland, A. M., Mair, J. T., and Bruce, D. F., *Glasg. med. J.*, 1955, **36**, 411.

Midnight Haemoptyses

SIR,—I read with interest the paper on Munchausen's syndrome by Dr. M. A. Peyman (March 5, p. 699). In the past five years I have come across three patients whose details might interest your readers. A timely recognition should curtail the anxieties of doctors at the casualty departments. All three patients were admitted at midnight with ? massive haemoptysis.

Case 1.—Mr. K, a middle-aged sailor with a strong Canadian accent, was admitted at midnight to a hospital in North London in 1956. I received a phone-call from the casualty department of another hospital where no emergency bed was available. The patient was reported to be in a collapsed state due to a massive haemoptysis. The admission was immediately arranged and the patient was brought straight to the ward. On admission he appeared rather drowsy but still could answer questions. His blood-pressure was normal although he had a tachycardia. He had slight cough, but little abnormality was detected in the lungs. He had scars of operation in his abdomen and some deformity of his upper extremity due to an old fracture. He gave a history of pulmonary tuberculosis while in Bombay a few years ago. He remained very drowsy during the next day. No staining was observed in the sputum and the chest radiograph did not show much abnormality. On being further questioned on the alleged haemoptysis, he became irritated and discharged himself.

Case 2.—Miss M, an Irish lady about 35 years old, was admitted to a hospital at 4 a.m. in 1955. She was found collapsed in a street with a blood-stained handkerchief by her side, and she gave a history of pulmonary tuberculosis in Ireland. Next morning she reaffirmed the history of massive haemoptysis, but no staining was observed in her sputum. She became abusive when doubts were expressed regarding her haemoptysis and the blood in her handkerchief and discharged herself. About 18 months later this woman turned up at the same hospital at midnight with another ? massive haemoptysis. This time she posed as a dumb and partly deaf person and answered questions in writing. She told that she had recently been sent out from a sanatorium where she was having treatment for pulmonary tuberculosis. The immediate chest radiograph showed little disease. As soon as I saw her, I reminded her of our previous acquaintance. She became abusive (on paper, of course) and threatened to sue me. However, she disappeared quietly before my next visit to the ward.

Case 3.—Mr. MacG, aged about 60 years, was admitted to a North London hospital at midnight as an emergency in 1956. On examination he was dyspnoeic but of good colour. He had generalized rhonchi and crepitations. An immediate chest radiograph showed slight fibrotic disease in his right upper zone. Next morning no staining was observed in the sputum, but he disappeared before any further investigations could be undertaken. Three days later I received a letter from a hospital in the Midlands, where he was then admitted with a similar story. By the time I answered their letter the patient had disappeared again. Only a few days ago I met him again at the present hospital. He had been admitted with a history of massive haemoptysis. As before, no staining was noticed in the morning specimen of sputum. I recognized him and introduced myself to him, reminding him of our previous encounter. He soon became abusive and was discharged.

All three patients had strangely similar stories of massive haemoptyses at midnight, but these were never confirmed. Case 3 had a few minor episodes in the past and he must have noticed the worries of the attending doctors. He had attended quite a few hospitals already when I first saw him. Cases 1 and 2 could give very good accounts of their illnesses in the past and the many investigations undertaken. Since haemoptysis is a serious complaint, these patients are usually admitted. A tired casualty officer is probably most likely to admit these cases in the early hours of morning without many cross-questions. For obvious reasons, they avoid admissions in the same hospital during a period of 12 to 18 months. Once admitted they are assured of full board and lodging for the next few days while all the expensive investigations are undertaken.

My thanks are due to Dr. J. Wallace Craig, who prompted me to report these cases, especially Case 3 in this series.

—I am, etc.,

Whittington Hospital, London, N.19. SAMIR K. GUPTA.

Carcinoid Tumour and 5-Hydroxytryptamine

SIR,—The case of a metastatic argentaffinoma secreting 5-hydroxytryptamine as reported by Mr. H. R. I. Wolfe and his colleagues (March 26, p. 925) was very interesting, and caused me to reflect upon a patient whom I saw some two or three years ago.

A boy aged 12 was admitted to hospital with a typical history and clinical signs of acute appendicitis, apart from bilateral subconjunctival haemorrhages which almost obscured the sclerotics. At operation, through a grid-iron incision, a gangrenous appendix was visualized. At the base of the appendix there was an intramural annular thickening which caused compete obstruction of the lumen. An uncomplicated appendicectomy was performed, and histological examination revealed the tumour to be an argentaffinoma. Following the operation, the patient made an uneventful recovery, and gradually the eyes returned to normal.

This is the only case of acute appendicitis I have seen with these ocular changes, and also the only case caused by a carcinoid tumour. Regrettably, no laboratory investigations were undertaken to discover whether there were any abnormal 5-hydroxytryptamine levels in the blood, but I have often tried to explain the fragility of these conjunctival blood-vessels.—I am, etc.,

Bognor Regis, Sussex. J. N. GRAHAM-EVANS.

Contrecoup Fracture of the Sternum

SIR,—I found the medical memorandum by Mr. Miles Fox on contrecoup fractures of the sternum (March 26, p. 935) of particular interest, as I have a case, almost similar to the one he describes, under my care at present.

On March 12 I was called to a shop to see one of my patients who had "cut her head." I found the patient in good shape with a cut on her occiput, but complaining bitterly of pain high up on her sternum. The pain, tenderness, and slight swelling left no doubt that she had fractured her sternum. She refused to be taken to hospital, so I took her home, stitched her head, and got her comfortably settled in bed.

She was a woman of 70, and was ascending a thickly carpeted stair when a party of people in front caused her

to hesitate. She lost her balance and fell backwards down three steps, striking her head against a radiator on the left side of the landing at the foot of the stairs. She had a linear vertical cut centrally over her occiput one and a half inches long and a similar cut through the felt and band of the hat she was wearing at the time. Her head had obviously struck the edge of one of the sections of the radiator. She was wearing a silver-bar brooch on her breast. This was badly bent, and she had a small cut under her chin. *X*-ray examination three days later confirmed the fracture, which was similar to the injury sustained in the case described by Mr. Fox. A transverse fracture one inch below the manubrium with backwards displacement of the upper fragment. Strapping was applied in hospital, but this was removed three days later at her request as she said she had been much better without it. There was little general upset, and she was getting about before the end of a week, though four weeks after the accident she has still considerable pain and tenderness over the sternum.

Whatever other factors played a part in the mechanism of this fracture one has evidence of the acute ante-flexion of the cervico-dorsal spine and the pressure of the chin on the upper part of the chest wall, by the injury to the chin and the damaged brooch.—I am, etc.,

Perth. JAMES SIMPSON.

High-pressure Salesmanship

SIR,—I would like to add my quota of experience of the present excessive postal advertising with which we are afflicted. In February I took a holiday from the daily task of opening these advertisements and accumulated an impressive pile which I have now counted. It was about 13 lb. in weight; 190 of them had a 2d. stamp and 15 had 3d. to 1s. 3d. stamps. This total of 205 works out at almost 9 per weekday; and, if they cost an average of 6d. plus postage, my yearly total is about £90. As this total is multiplied by all the doctors on the mailing-list, it appears to me that several million pounds a year are going into our waste-paper baskets.

If we were sent an occasional booklet by the drug firms I think there is more chance that it would be looked at, as well as not causing this daily annoyance.—I am, etc.,

Alnwick, Northumberland. R. A. BLAIKLOCK.

SIR,—The impact of the National Health Service upon the pharmaceutical industry was responsible for launching a bombardment of proprietary drug literature of such intensity that it has now kindled something like an inferno of therapeutic propaganda. Various correspondents to the weekly medical journals have already expressed this opinion, though not in such lurid language. Our personal views are based on an analysis of one year's postal influx of commercial "materia medica."

We listed the mail under the following headings:

Sealed envelopes	20
Unsealed, plain envelopes	736
Unsealed envelopes, with outside advertising matter	112
Postcards	214
Folded postcards (i.e., with partly-concealed advertising matter)	21
Total	1,103

The numbers, incidentally, represent approximately one-half of the actual total, since we pooled the mail received by both of us. The monthly total was lowest in August (59) and highest in January (113). During nine months of the year the number of communications was consistently between 90 and 100. Mail was received from 71 drug firms. (One of these sent no less than 167 communications—all concerned with only five products.) Other firms wrote to us on, respectively, 108, 47, 46, and 43 occasions. The total number of advertising items (excluding trade journals, therapeutic indices, price lists, sample request cards, blotters, etc.) was 1,425. These ranged, in format, from single sheets to extensive pamphlets and booklets.

We tried to classify the type of drug advertised, according to the method adopted in the *British National Formulary*, and found this confusing because of various multi-applicable products. We also listed them in order of advertising frequency—and in the kind of groups that we think of, in everyday practice—namely:

Sedatives and tranquillizers	189
Antibiotics	137
Cortisone preparations	77
Analgesics	69
Antihypertensives	62
Intestinal antispasmodics	61
Nasal drops and sprays	52
Antihistamines	49
"Benzedrine" derivatives, slimming drugs, etc.	32

We devised a system of criteria about the standard of information given in commercial drug literature under such headings as "indications and contraindications," "side-effects, dosage, and method of administration," "pharmacology," "chemical composition," "bibliography," and "price." 5% of the advertisements gave no indication of what the drug was intended to be used for; only 10% referred to side-effects or the absence of side-effects; 20% entirely ignored dosage instructions; and in no less than 60% there was no mention of prices. Chemical composition and pharmacological properties are perhaps of less immediate import, depending on how you feel about drugs in general.

But what, in fact, do doctors want to know about any new drug? The answer is simple: What is it for?—and: Is it better for that purpose than the drug we have been using? From the manufacturers' point of view, naturally, their own product is always an improvement on somebody else's. But how are we poor victims going to select the best out of 60 or 70 anticholinergic agents, for example? In short, we are very tempted to follow the example of one of our colleagues who tips all his drug mail into a hundredweight sack and eventually adds it to a compost heap in the garden, where it ripens into an excellent manure for his roses.—We are, etc.,

C. G. WARNOCK.
W. G. M. BELL.

Newtownards, N. Ireland.

Now Market Research

SIR,—Many doctors will have received an important-sounding letter from a "research" organization with an enclosed questionary. The covering letter tells us that we are being approached on behalf of a firm (unnamed) active in the pharmaceutical industry. The purpose of the inquiry is to discover our opinions as to the value of treatment for certain specified conditions, and also to inquire as to what preparations we prescribe for a given list of conditions.

It would require some credulity to believe that, if Messrs. A. & Co. commissioned this piece of impudent research, and the inquiry revealed an overwhelming vote for a product of Messrs. B, this would be published as a piece of detached scientific evidence in support of B's product. More likely that Messrs. A would be

inclined to manufacture the identical product, wrap it in different "cellophane," and market it under a different name.

This is not research, and we should object as a profession to being used as the objectives of a commercial market-research organization. Let them conduct their market research in the market, not in our surgeries. The growing tendency by some drug firms to elicit information directly from general practitioners is something we ought to consider rather urgently. Might the growing list of inducements make some of us feel under some obligation to co-operate—was the last golf party, meeting and reception, lecture plus refreshments, etc., so good that the warm glow is still in our hearts when the representative follows up? I feel that we may well be at a critical point in our relationship with the big drug houses, and unless we demand a halt to the glossies—parties—student entertainments, etc., we may find ourselves involved more and more in these degrading stunts. Let us act as a learned profession should, and recover some lost dignity.—I am, etc.,

Liverpool, 8. CYRIL TAYLOR.

Heroin in Coronary Thrombosis

SIR,—Dr. G. H. Jennings in his letter (March 26, p. 967) recommends the use of heroin as a routine for the severe pain of coronary thrombosis, on the grounds that it seems to lessen the nausea and vomiting not infrequently seen with morphine in these circumstances. I believe a more appropriate morphine-substitute for the relief of severe pain in coronary thrombosis is dihydromorphinone hydrochloride ("dilaudid") in a dose of 1/32 to 1/16 gr. (2 to 4 mg.) subcutaneously, or intravenously when shock renders absorption unreliable. It is about three times as powerful as morphine,[1] and vomiting is uncommon after injection.[2] It is less likely to cause addiction than morphine, and very much less likely than heroin. Owing to the natural history of coronary atheroma and thrombosis, more than one injection will often be required.—I am, etc.,

Hailsham, Sussex. R. NEVILLE.

REFERENCES

[1] Hale-White, W., *Materia Medica Pharmacology and Therapeutics*, edited by Douthwaite, A. H., 31st ed., 1959, p. 180. London.
[2] Cruikshank, A. G., *Pocket Prescribing*, 16th ed., 1956. Edinburgh.

Promazine Overdosage

SIR,—Drs. John MacVicar and Margaret H. Murray (February 27, p. 595) report on a trial of promazine in labour. They comment on a case of promazine overdosage in a barbiturate addict recorded by Buckmaster in 1957.[1] The dosage of promazine in this case was 2,200 mg. The main point that he makes is the depth of unconsciousness without respiratory depression. In view of the large amounts of "tranquillizers" now being used cases of this kind may well become more frequent, and we therefore think it worth while to record the following case:

A pensioner of 60 was admitted having taken about fifty capsules, and these were later identified as "prozine." Each capsule contains 25 mg. of promazine and 200 mg. of meprobamate, so that the total dosage taken was approximately 1,250 mg. of promazine and 10,000 mg. of meprobamate. He had had a partial gastrectomy seven years ago, and this was followed by vagotomy a year later for persistent abdominal pain. He had made two previous suicidal attempts, and he had been treated with E.C.T. in the past.

On admission he was deeply unconscious. The pupils were normal in size but did not react to light, and there was a divergent squint. His limbs were flaccid and all tendon reflexes were absent. The carotid pulse was regular at 90 per minute, but the arterial pulse in the arms was unrecordable. In spite of this his hands were warm. Respiration was normal in depth and rate. After an initial stomach wash-out, a polythene cannula was inserted into the subclavian vein. An infusion of dextrose saline containing 4 mg. noradrenaline to the pint was started, and his blood-pressure rapidly rose to 100/60. Subsequently the concentration of noradrenaline had to be increased to 16 mg. per pint in order to maintain the blood-pressure at this level. Twelve hours after admission he was able to swallow sips of water and spontaneous movements began after twenty-four hours. Thirty-six hours after admission he was awake and rational. The infusion rate of noradrenaline was gradually decreased and finally stopped fifty-two hours after admission.

Meprobamate is virtually non-toxic and no hypotensive effects have been recorded, so that the clinical appearances can be assumed to be due to promazine. The most marked differences between this patient and those having had an overdose of barbiturate were: (1) The absence of respiratory depression even with deep unconsciousness. (2) The total absence of peripheral pulses with an obviously high skin blood-flow. It is not possible to be certain that noradrenaline was responsible for recovery in this case, but if the blood-pressure had remained unrecordable for any length of time survival would seem unlikely.

We would suggest that the possibility of promazine or chlorpromazine should be considered in cases of drug overdosage and that, if severe, intravenous infusion of noradrenaline is the correct treatment.—We are, etc.,

W. HINDLE.
D. NEGUS.

Royal South Hants Hospital, Southampton.

REFERENCE

[1] Buckmaster, J. F., *Brit. med. J.*, 1957, 1, 1242.

Speech Therapy and Child Guidance

SIR,—On the face of things our letter (April 2, p. 1054) deserved the criticism it has received (April 23, p. 1275) from several writers among whom are one or two of my teachers. The contention that child psychotherapy should ideally remain in the hands of those who have had or are receiving adequate training has undeniable validity which I do not challenge. It is just possible that there are in the London area sufficient fully trained people to give this some appearance of reality. In the rest of the country, with four-fifths of the total population, however, child psychiatrists are very thin on the ground, and child psychotherapists even more so.

The actual position as regards speech therapists is that they are treating, attempting to help, or whatever one calls it, enormous numbers of children, and in a substantial proportion of these the speech defect is but one manifestation of an emotional disturbance. This work they do with the concurrence and warm support of medical officers of health, education authorities, and many assistant school medical officers. There is no possible prospect of being able to say that we will provide fully trained therapists to treat all these children, and I think we are faced with two alternatives. In the first place, we could ignore or even discourage this work done by speech therapists. If we did that the speech therapists would continue what they are doing as at present, and informed psychiatric opinion would be more disregarded and have less say in their councils than at present. The second alternative is what I am suggesting—namely, that we

should invite the speech therapists to consult freely with the child psychiatrists, and should offer to provide not only consultation with them but also tutorial sessions related to the actual cases which the speech therapists are handling.

Provided that the high standard of selection of child psychiatrists is maintained, I consider that to disseminate our skill and experience among the speech therapists, who are our colleagues, in this way will raise the standard of the work they are doing, and will at the same time enhance the authority of the child psychiatrist in spheres which are allied to our own.—I am, etc.,

Uffculme Clinic,
Birmingham, 13.

DAVID T. MACLAY.

SIR,—The letter from Dr. David T. Maclay and his colleagues (April 2, p. 1054) raises several important issues. It prompts a response on two scores. First, the clinical conclusions to be drawn from the rapid amelioration of two very recent cases of children suffering from severe and long-standing speech defects (both previously treated by speech therapy, in one instance of a prolonged and intensive nature), and, secondly, the burden cases such as these place on the taxpayer. Because all defects of speech, regardless of their causation, are classed as a "handicap," the statutory provision of speech therapy centres has been made. This fact helps largely to explain why so few of these children find their way to a psychiatrist—i.e., they are automatically directed to these centres.

A parallel to the rationale whereby no directive distinction is made between organic defects, the unchallenged sphere of the speech therapist, and *impediments* of speech of psychogenic causation, would be if chronic "defective gaits" were automatically referred to the physiotherapists, regardless of whether such disturbances of walking were hysterical, postural (either psychogenic or organic), neurological, or due to phobias. The statutory situation of to-day with regard to the management of speech defect differs hardly at all from the absurdity of the foregoing. However, to continue the parallel, your correspondents suggest that, as an advance on present practices, in so far as it is determined that the "defective (verbal) gaits" are non-organic, accordingly the physio- (speech) therapists should either work more closely with psychiatrists or gain competence in "psycho- or play therapy." Not only do your correspondents seem to be unaware of the ever widening professional chasm between these two last-named levels of training and approach, but they confidently designate rhinophonia, dysphonia, and dysarthria as organic, which they only *sometimes* may be, in contradistinction to the more obvious psychogenic disorders of speech. Such confusions of simple facts, even when impressed into a good cause, do it a great disservice. The stage of knowledge has now been reached when, to continue the parallel with physiotherapy, not only are hysterias and phobias recognized as psychogenic, but their psychodynamic differences are also known. The consequence is that their unconscious symbolic significance to the patient, thanks to a psycho-analytic training, can be both determined and curatively conveyed.

A brief description of the two recent cases of speech defect will make the position clearer. An 8-year-old boy, suffering from such a degree of stammer, dyslalia, and dysphonia as to have become ever more explosively incomprehensible since the beginning of school life, worsened with the institution of speech therapy. Yet an improvement was to become apparent even after his first psychiatric interview, which now (eight interviews in four months) is very striking indeed. There is no longer any impediment of speech in conversation with his peers, and there is infinitely less (and then only in brief spasms) with adults. The reason is that he has been shown the style of his overall mechanism of "oppositionalism," whether of his apparatus of phonation or of tongue-positioning. Its underlying meaning—namely, marked counter-phobic aggressivity against (phantasied) talion threats—has also been conveyed to him. *Pari passu*, his uninsighted, well meaning, but "bull-dozing" mother has been shown why it is that her lively and anxious son needs coaxing, rather than shoving, into co-operativeness.

The other case is even more striking. A 13-year-old boy had such a severe speech defect including rhinophonia, until one month ago, as to have been wholly incomprehensible on referral, as is his grossly speech-defective father. The father could not come to the clinic because he is crippled. Instead the sister of his dead wife—i.e., the boy's aunt, brought the patient. The aunt is known to me through her part-time employment (non-medical) as a sensible and kindly person. When talking, not only did the patient leave out all intermediate words such as "this" (or, as it turned out, any word involving tongue movements of the kind required for "s," "d," "t," etc.), but those words he attempted to enunciate were incomplete—i.e., "raft" became "wraaf." Three main items were noticed: (1) his lips were kept parted and immobile, (2) his tongue was seen not to move at all, (3) he had the dentition (and as was then confirmed, the palate) of a chronic thumb-sucker. It was explained to him that he talks *as if* his thumb were perpetually in his mouth, at rest in its precisely fitting furrow in the palate. All that was advised was that he should read out loud, syllable by syllable, so that his spelling, which follows his pronunciation, would improve, and, of course, to desist as much as possible from thumb-sucking, whether phantasied or actual. Two weeks later, he came back a changed boy, enunciating *all* words quite comprehensibly to the accompaniment of a wide, delighted grin. The school staff, the divisional medical officer, and others are all astonished by the seeming "miracle." He has already been the institutionalized subject of years of intensive and expensive speech therapy. The outlook seemed especially unpropitious, in that he must have closely identified himself with his speech-defective father, if not in the precise style, then at any rate in the net result of incomprehensibility.

While it is realized that there are not enough psychiatrists to investigate all cases of psychogenic speech defect, and that many children so affected do profit, even verbally, from the kindly and individual attention of a patient adult, these are not reasons enough either for the befogging of available knowledge, nor for the undiscriminating expenditure of public funds.—I am, etc.,

AUGUSTA J. BONNARD.

East London Child Guidance Clinic,
London, E.1.

Undescended Testicle

SIR,—The paper by Drs. Barbara Ward and W. M. Hunter (April 9, p. 1110) and the associated comments still show how far we are from a real understanding of the subject. It shows also how pertinent are Mr. C. G. Scorer's remarks (April 30, p. 1359) on what is an "undescended testicle." The evidence given by Drs. Ward and Hunter is extremely difficult to interpret, as Mr. Barry O'Donnell suggests (April 30, p. 1360), and without additional information is not of great value. It does, however, give some support to Mr. Scorer's published observations, and viewed in conjunction with his work can be considered of value.

With reference to Mr. Scorer's views on the cremaster muscle in the testicular descent of puberty, I can make relatively few helpful suggestions on human subjects. Experimental work on rats, however, does indicate that testicular descent around birth (which occurs then in the rat as in the human) is a very different process from

that taking place at puberty. At puberty the important factors are a generalized increase in size of all the sexual structures, including the cremaster muscle. Although hormones play a very important part in this size increase, no change takes place in the cremaster muscle unless it is associated with the bulk of a testis or an artificial testis. These hypertrophic changes in the cremaster muscle occur even if the genito-femoral nerve is cut.

My views in man are that at puberty the cremaster muscle increases in size together with the testis under gonadotrophic influence, and appears to become less active. It is, however, difficult to dissociate the effects of increased testis weight when considering relative excitability. If the testis and cremaster muscle are observed with increasing age in the adult it appears that the muscle continues to become less active and the testes and scrotum tend to become more dependent. The testis and its coverings even become attached to the floor of the scrotum, and often derive a secondary blood supply via this route from the scrotal wall. The low excitability of the cremaster muscle observed by Mr. Scorer soon after birth may well be associated with the tail-end of the maternal hormonal influences which have existed over the foetus until birth. The testis shows marked interstitial cell activity until shortly after birth, but then this wanes until puberty.

Mr. Denis Browne's direct attacks on anatomists (May 7, p. 1428) must bring some comment from the one who did the quoted work on the gubernaculum of the pig, but who it is suggested has shown little interest in human anatomy. Having been in correspondence discussion with Mr. Browne on two previous occasions in this journal (1957, **1**, 1420; 1958, **2**, 165) on the very matter which he suggests is neglected, I see no point in maintaining a useless argument. I feel, however, that Mr. Browne should realize that some anatomists do consider the living human, not only in the clinic and laboratory, but even in the operating theatre. At operation I have stimulated the genito-femoral nerve and brought the testis of pre-pubertal boys up into the inguinal canal, so that most of the gland passed the external ring. I do not claim that this is the only response, but I do claim that (1) testes are sometimes found in the inguinal canal at operation which are free to pass out into the scrotum, and (2) that it is experimentally possible in some cases (under general anaesthesia) for the immature testis to pass into the canal. My only quarrel with Mr. Browne on this question is with his refusal to accept that in some cases testes can pass into the inguinal canal.

So far as avoiding a showdown is concerned, I for one anatomist would be delighted to accept Mr. Browne's offer if it were intended as a serious invitation. Perhaps at the same time I could interest him in the anatomy and physiology of testicular descent in the human.—I am, etc.,

London, W.C.2. K. M. BACKHOUSE.

Psychotherapy in Migraine

SIR,—In their paper "Psychotherapy in Migraine" (April 9, p. 1084) Drs. Richard A. Hunter and Ian P. Ross make an important point that seems to have escaped many clinicians. They say, "It seems almost as if it were more important to ask patients 'Who or what is your headache?' rather than 'When or where?'" This does indeed seem to be the case at times, particularly, in my experience, in those subjects with undiagnosed pain who are referred to the psychiatric clinic after extensive medical or surgical attention. In some of these cases I have found that the most elementary questions of human relationships have not been considered, and so the simplest and, at times, the most remediable of psychopathology has not been detected.

When a patient says he has a pain he may mean many things, and it may be difficult to discover exactly what he does mean. However, there are some patterns of meaning which are probably more common than is generally recognized. For example, mourning reactions which have not been successfully resolved may produce delayed results months or years later. They may present as a depressive state, but the sole complaint may be pain. Obscure periodicity of symptoms such as pain may at times be understandable as expressions of anniversary reactions in relation to past events, such as pathological mourning reactions, of which Drs. Hunter and Ross give typical examples. Pain may represent the identification with the symptom of an ill or dead parent or spouse, or the pressure of past conflict that has hitherto been too "painful" to bear. Psycho-analysts use the term "internal object" to refer to an internalized or ingrained pattern of past relationship. This metaphor is particularly useful, as it conveys how certain mental organizations tend to function as discrete sub-personalities, and sometimes to behave as concrete objects within the boundaries of the body image. The physiological correlates of these processes are as yet imperfectly understood, but enough is known of them to indicate that the dichotomy "psychogenic" and "organic" pain is an unsatisfactory one.

How common this type of syndrome may be is not known, and it will remain so as long as physicians fail to ask themselves, and occasionally their patients, such apparently ingenuous questions as "Who is your pain?"—I am, etc.,

London, W.1. MURRAY JACKSON.

Care of the Old

SIR,—We wish to congratulate you on your leader on the care of the old (April 23, p. 1261). This presented in summary the present problems.

We feel that your criticism of elaborate municipal clinics does not apply to our joint effort at Rutherglen. Here we have attempted to integrate the activities of the geriatric unit, the local authority, the general practitioner, and voluntary effort. Without this co-ordination complete success in promoting the health of the elderly is impossible. The centre operates from an already existing local-authority clinic, and no money has been required to provide expensive equipment. Our relations with our local general practitioners have been excellent; the centre could not function for one day without the support and co-operation of the general practitioners, and our sole supply of patients is through the family doctor. This centre is in essence a projection of the geriatric unit into the community and allows the opportunity to practise preventive medicine in a positive fashion.[1] Since 1952 over 1,200 new cases over 55 years of age have been seen at our centre, and we are certain that no function of the general practitioner has been usurped.—We are, etc.,

NAIRN COWAN.
FERGUSON ANDERSON.

Public Health Clinic, Rutherglen.

REFERENCE

[1] Anderson, W. F., and Cowan, N. R., *Lancet*, 1955, **2**, 239.

Obituary

CECIL H. M. HUGHES, O.B.E., M.B., B.S.
F.F.A. R.C.S.

Dr. Cecil Hughes, consulting anaesthetist to King's College Hospital, died at his home in Hove, Sussex, on May 2. He was 81 years of age.

Cecil Hugh Myddleton Hughes was born in London in 1879 and educated at Westminster School and at the Westminster Hospital, qualifying in 1903 and graduating M.B., B.S. two years later. After holding the posts of house-physician and resident obstetric assistant he was appointed administrator of anaesthetics to Westminster Hospital, a post that he held until 1913. In that year he joined the honorary staff of King's College Hospital as assistant anaesthetist, becoming senior anaesthetist and lecturer on the retirement of J. F. W. Silk in 1921. When Hughes retired in 1936, two years before he was due to do so under the age limit, he was appointed consulting anaesthetist. He was also anaesthetist to the Seamen's Hospital, Greenwich, the Samaritan Free Hospital, the National Dental Hospital, and the Bethlem Royal Hospital. During the 1939 war he returned to work at the Leatherhead Emergency Hospital in the King's sector.

Hughes saw service in both the Army and the Royal Navy. While still a junior medical student he joined the South African Field Force and served in the Imperial Yeomanry Field Hospital during the South African War. He was captured by the famous Boer general de Wet, but managed to escape. In the first world war he was appointed consultant anaesthetist to the Navy, with the temporary rank of surgeon-commander, and served at the Royal Naval Hospital, Chatham, with a famous King's surgeon, Sir Watson Cheyne. Hughes is said to have anaesthetized Admiral Jellicoe; the two became firm friends, and often dined together in after years. At the end of the war he was appointed O.B.E.

Cecil Hughes was both secretary and president of the Section of Anaesthetics of the Royal Society of Medicine. In 1930 the centenary of the death of Henry Hill Hickman was commemorated, and, as secretary of the Section, Hughes was made responsible for the arrangements and for the collection of donations. He was always proud of the fact that it was largely through his own efforts that the Hickman medal, awarded for outstanding service to anaesthesia, was instituted.

An anaesthetist of the old school, Hughes practically confined himself to the Clover's inhaler, chloroform–ether mixture, and spinal analgesia. He refused to employ deep anaesthesia, and it was not unknown for his surgeons to comment somewhat forcibly upon this idiosyncrasy. Yet he was an artist in his own technique, and there must be many of his old students who can recall the results that he obtained by the meticulous dropping of almost infinitesimal quantities of chloroform-and-ether mixture upon a Schimmelbusch mask covered with a single layer of lint. He was elected a Foundation Fellow of the Faculty of Anaesthetists of the Royal College of Surgeons of England in 1948.

"Daddy" Hughes was a quiet man with a very gentle manner: he was a good teacher who took a real interest in his students. Perhaps his outstanding characteristic was his perfection of manners as a host. At the little dinners which he gave to his house anaesthetists at the Bath Club, usually before a meeting of the Royal Society of Medicine, he saw to the comfort of his guest with an easy and eager courtesy that will long be remembered by those who were privileged to experience his hospitality.

Cecil Hughes married Anne Athol, daughter of J. H. Stewart, of New South Wales, and widow of Dr. W. Rivers Pollock. His wife died in 1958, a sad loss from which he never entirely recovered.—F.F.C.

MAX von LAUE, Ph.D., D.Sc.

Professor Max von Laue, until recently head of the Max Planck Institut für Structurforschung in Berlin, died there on April 23 at the age of 80 as a result of a car accident. His work leading to what is now known as *x*-ray crystallography won him the Nobel Prize for physics in 1914.

Dr. M. F. PERUTZ, F.R.S., director of the Molecular Biology Research Unit of the Medical Research Council, writes: Von Laue's life shows the far-reaching effect of a single brilliant idea on the development of science. In 1912 a colloquium on the interaction between crystals and electromagnetic waves was held at the University of Munich. Von Laue, then a lecturer in theoretical physics, is said to have wondered what would happen if the wavelength of the radiation were reduced to the size of the atoms, and to have predicted that the regular arrangement of atoms in a crystal would act as a diffraction grating for the waves. In opposition to Röntgen and others, who regarded *x* rays as streams of particles, von Laue was convinced that they were electromagnetic waves, and had reason to believe that their wavelength would be of the right order to produce just the diffraction effects he had thought of. At his suggestion, Friedrich and Knipping illuminated crystals of copper sulphate, zincblende, and others by a narrow beam of *x* rays and placed photographic plates behind the crystals. To their delight the developed plates showed striking diffraction patterns, confirming von Laue's prediction and proving the wave nature of *x* rays. Von Laue proceeded to work out the theory of diffraction by three-dimensional gratings, but failed to unravel the atomic arrangement in zincblende, partly because Groth, the leading German crystallographer, had given him the wrong advice concerning its structure.

It was left to a research student at Cambridge, W. L. (now Sir Lawrence) Bragg, to work out the atomic arrangement in common salt from its *x*-ray diffraction pattern. This was the beginning of *x*-ray crystallography, a branch of science unknown to the non-specialist, which has contributed more than any other to the elucidation of the atomic structure of matter. In the 'twenties and 'thirties it brought coherence into the sciences of mineralogy, metallurgy, and inorganic chemistry. Its impact on biochemistry and medicine started with the work on protein fibres, in which W. T. Astbury played a prominent part, and reached a peak with Dorothy Hodgkin's establishment of the chemical structure of penicillin and vitamin B_{12}. In the 'fifties, *x*-ray crystallography has taken a new leap forward, and is now helping us to understand the molecular basis of life. The α-helix which L. Pauling recognized as the structural basis of proteins, and J. D. Watson and F. H. C. Crick's double helix of D.N.A., which taught us what genetic replication means in chemical terms, were two crystallographic discoveries of far-reaching importance. Most of what we know to-day about the general principles of virus structure comes from *x*-ray crystallography. Its latest success is the unravelling of the structure of two proteins, myoglobin and haemoglobin, by J. C. Kendrew, myself, and our colleagues on the staff of the Medical Research Council.

We had looked forward to welcoming von Laue here at the forthcoming tercentenary celebrations of the Royal Society, and to showing him how the tree he had planted still flourished. It will be sad to miss him.

D. R. HARRIS, M.R.C.S., L.R.C.P.

Dr. D. R. Harris died on April 6 at his home in Falmouth at the age of 80. He and his father had between them practised in the town for nearly 100 years.

Dudley Raymond Harris was born on July 28, 1879, the son of Dr. A. B. Harris. He studied medicine at the Middlesex Hospital, qualifying in 1904. After holding house appointments at his teaching hospital, at the Brompton Hospital, and at the Worcester General Infirmary,

he joined his father in practice in Falmouth, where he held many offices, including those of honorary surgeon to the Falmouth and District Hospital, medical officer of health, and police surgeon. During the first world war he served in France as a medical officer with the Tank Corps and the Highland Light Infantry.

Dr. Harris is survived by a widow and two daughters.

E. R. H. writes: The Harris family have been medical practitioners in Falmouth since the Crimean War. It is indeed sad that such a record of service to the community has come to an end. Dudley Harris was family friend and doctor, and for him no trouble was too trivial to warrant his care. A doctor of absolute integrity, he had no regard for financial reward. With all this went a great sense of humour. I remember his reflections on how chance may govern our lives. He recorded how his father, when serving in the Crimean War, heard of a vacancy in general practice in Market Street, Falmouth. This vacancy was unexpected, in that the resident doctor had to appear at Bodmin Assizes on a charge of the murder of his prospective mother-in-law. In his quiet dry way, Dudley Harris explained that this trial was, in ways, unique. The accused was allowed to assist at the necropsy carried out by a pathologist from Exeter, and, through some misunderstanding, disposed of the stomach and other important organs down the closet as they were passed to him by the pathologist.

Although retiring from active practice some four years ago, Dr. Harris retained an absorbing interest in medicine to his end. His friendly help and advice will be missed by many in Falmouth.

T. H. GUNEWARDENE, M.R.C.S., L.R.C.P.

Dr. T. H. Gunewardene, who practised in Colombo and was known especially for his work as a paediatrician, died on April 3, aged 71.

Theodore Hamnet Gunewardene, who was born on March 12, 1889, was educated in Ceylon and at King's College Hospital, London, where he took the Conjoint qualification in 1916. After holding resident posts in Salford and London, he returned to Ceylon in 1919.

Dr. STANLEY DE SILVA writes from Colombo: When the news of Dr. T. H. Gunewardene's death became known there must have been many whose minds passed back to their association with him over their illnesses or their children's illnesses, and perhaps even over the illnesses of their children's children. For having started nearly 40 years ago in a specialty which did not exist in Ceylon at that time, he plodded on against heavy odds in firmly establishing the specialty of paediatrics in this island, and therefore may be called Ceylon's pioneer paediatrician.

It was his good fortune while at King's to work under Sir Frederic Still—England's leading paediatrician. He was also most fortunate later when during the first world war he worked as a resident medical officer at the East London Hospital for Children, Shadwell (now known as the Queen Elizabeth Hospital for Children). It is interesting to see his son at present working at the same hospital. Returning to Ceylon with this unrivalled experience, he decided to confine himself to paediatrics in further practice. I remember him telling me that before he did so he asked for the advice of the two most senior doctors in Colombo at that time—Sir Marcus Fernando and Dr. S. C. Paul. They both strongly advised him against this specialty, which they said "had no scope whatever in Ceylon." His dogged determination, however, made him reject this advice, and he boldly started in Colombo and established the "Private Hospital for Sick Children." As years rolled by, he realized that children could be better looked after by the mother in the home than by outsiders in a hospital—and he paid less attention to hospitalization of children and came to regard the mother-and-home environment as the most important factor in management of children.

Besides his work in his consulting-room he took an active part in professional life, and was for many years an active member and secretary of the Independent Medical Practitioners Association. He was also a past-president of the Ceylon Branch of the British Medical Association. For twenty-five years he went on Sunday mornings to the Social Service League at Deans Road, Maradana, and examined and treated the poorest of the poor children there without any fees. He only gave up this work and his practice a few years ago when a crippling illness unfortunately made it impossible for him to work any longer.

There was more in him than skill: there was a large heart, a friendliness, a frankness, and a humbleness which made every man who met him love him. The people had confidence in him always. He could have died a richer man if he had encouraged his patients to turn up at his consulting-room for injections and bottles of medicine; instead he was more inclined to say that there was nothing the matter or very little the matter with a child, and all that the child needed was a morning's play on the beach. He always became a friend of the family wherever he went, and I am sure that many who consulted him during the last 40 years will admit that besides helping them in the illnesses of their children he was always a lovable friend and counsellor in their troubles.

He was a sound practical clinician whose opinion was sought and valued by his colleagues, even by those on the visiting staff of the General Hospital. Although he was only a practitioner he made a deep impression on those he came in contact with. He showed us the practice of medicine as a vocation; and, although we have lost a good friend and counsellor, we have gained from him a permanent portrait of a good man and a good physician.

K. DAMODARAN, M.B., B.S., M.R.C.P.Ed. D.T.M.&H.

Dr. Kesavan Damodaran, superintendent of the Central Hospital, Asansol, Bengal, died on January 12. He was 52 years of age.

Kesavan Damodaran was born on October 12, 1907, in Kerala, India. After taking a degree in physics at Madras University in 1928 he graduated M.B., B.S. in 1934. He then worked for a year as medical officer in the Maldive Islands, where his work on leprosy received high praise. After holding the post of house-physician in the Government General Hospital, Madras, he came to England and took the Conjoint qualification in 1939. After a period of general practice in Whitechapel he was commissioned in the R.A.M.C. and served in military hospitals in England, Scotland, and Malta, where he remained for two years. Later he went to Syria, Palestine, Egypt, and India, holding the rank of major. On release from the R.A.M.C. he went to Edinburgh for postgraduate study and took the M.R.C.P. of Edinburgh in 1950 and the D.T.M.&H. in 1951. While serving in the R.A.M.C. he carried out valuable investigations on infective hepatitis, and two of his papers on this subject were published in this journal.

On his return to India he was appointed chief physician at the Central Hospital, Dhanbad. Two years later, in 1954, he became superintendent of the new Central Hospital, Asansol, Bengal, and built this up into one of the best-known institutions connected with the coal-mines welfare scheme in India. He had also under his charge two regional hospitals and one tuberculosis clinic in Ranigunj coalfield and two regional hospitals in Madhya Pradesh coalfield. He took a keen interest in industrial medicine, undertaking much research on pneumoconiosis, and he was a member of the three-man committee appointed to advise the Government of India on certain points connected with the Workmen's Compensation Act. His untiring and selfless devotion to his work and his qualities of head and heart attracted people to him not only as a physician but as a friend and counsellor. For two consecutive years he served

as president of the Asansol Branch of the Indian Medical Association.

Dr. Damodaran often remarked that the best education was to be had by travel. He loved and admired beauty and nature and was deeply religious. With his death in the prime of life the medical profession has lost a physician of sound judgment, an efficient administrator, and a man who was loved by all who came into contact with him. A colleague has written of him: "His erudite knowledge, his sombre serenity, and his dignified demeanour impressed me most and evoked in me a feeling of respect and friendship for him."

He leaves a widow, well known as an educationist in Madras State. Their friends in the United Kingdom will wish to extend to her their sympathy.

We record with great regret the death of Mrs. Elisabeth R. Dougal Callander, wife of Mr. L. Dougal Callander, Treasurer of the British Medical Association. Mrs. Dougal Callander took an active part in the civic life of Doncaster, having been mayor of the borough in 1956–7.

Medical Notes in Parliament

University Teachers' Salaries

The Chancellor of the Exchequer has accepted the opinion of the University Grants Committee, based on representations from the Association of University Teachers and the advice of the Committee of Vice-Chancellors and Principals, that a revision of the salaries of academic staff at the universities is necessary. Announcing his decision in the Commons on May 3, he said that the University Grants Committee had submitted recommendations concerning the salaries of non-medical and preclinical staff, adding, "In so doing, they have said that they are considering the position of clinical staff in relation to the conclusions of the Royal Commission on the Remuneration of Doctors and Dentists, and will in due course submit recommendations under this head."

Two Bills Leave the Commons

The Radioactive Substances Bill completed its passage through the Commons on May 4, when the Parliamentary Secretary to the Ministry of Housing and Local Government indicated that it was the Government's intention to increase the inspectorate in order to deal with the whole range of radioactive use, and that the Government Chemist was setting up an additional laboratory. He also gave a warning that it would be some little time before the appointed day for the operation of the Bill could be named. The Minister, Mr. H. BROOKE, added the prophecy that one day further legislation would be required in the light of additional knowledge that would become available. Meanwhile the Government regarded the statutory requirements of the Bill as the minimum, and wanted to improve on them.

This Bill goes back to the Lords only for assent to amendments made in the Commons. The Professions Supplementary to Medicine Bill, which also got its third reading on May 4, has to begin its course through the Lords. The principal change made in it in the closing stages was to exclude from its provisions speech therapists. The Minister of Health, moving the amendment to secure this, read correspondence between himself and the College of Speech Therapists. He said they clearly and unequivocably objected to inclusion, and therefore he was honouring the undertaking he gave on the second reading that inclusion should be by conviction and not compulsion. He did not alter his original view that it was "unfortunate" that they insisted on exclusion; and Dr. EDITH SUMMERSKILL (Warrington, Lab.) added that if she had not been associated with these negotiations she would not have believed that any professional body would have refused to be associated with the Bill. A consequential amendment to the First Schedule reduced the number of medical members on the proposed council by one, in order, as the Minister explained, to maintain the numerical equality between the representative and the medical members. The Bill, of course, left the Commons without any subpoena powers, pending the report of the Simonds Committee on the powers of disciplinary tribunals. The Minister indicated that if the report was received relatively soon the Bill could be amended in the House of Lords. If the report should call for legislation in a wider and more general field than these supplementary professions, then the general legislation would govern the proceedings of these disciplinary committees.

QUESTIONS IN THE COMMONS

Accident-proneness of Motorists

Mr. R. GRESHAM COOKE (Twickenham, Con.) asked the Minister of Transport on May 4 what study had been made, and what further study was being contemplated, of accident-proneness in relation to road safety. Mr. JOHN HAY, Parliamentary Secretary, said that investigation of the question whether any relationship could be established between the characteristics of individual drivers and the number and type of accidents which they sustained was on the long-term programme of the Road Research Laboratory. Some limited studies had been made by the laboratory in collaboration with the Medical Research Council. The Ministry would look into the possibility of an extension of research in this field by the appropriate bodies. Mr. COOKE said that investigations in the United States and in Germany tended to show that about 20% of drivers were responsible for about 80%. If, in collaboration with the insurance companies, this could be confirmed, it might be possible to apply corrective measures to the 20%. Mr. HAY replied that the American experience was by no means conclusive, but they were asking the Road Research Laboratory to look into the possibility of further research.

Doctors' Car-parking Needs

Mr. ERIC JOHNSON (Manchester, Blackley, Con.) asked if the Minister would make regulations to facilitate parking of cars by doctors when visiting their patients in parking-meter zones.

Mr. ERNEST MARPLES: The installation of parking meters has the effect, among others, of making visits in the area easier, I should not consider myself justified, in the circumstances, in creating such special privileges as suggested, even for members of the medical profession. Mr. JOHNSON pointed out that it was virtually impossible for doctors to make use of metered spaces because they were already full. Would the Minister consider the possibility of making regulations for doctors when visiting patients on the same lines as those for commercial vehicles? If not, what advice would he give doctors on the best way to make their rounds? Mr. MARPLES replied that the B.M.A. had a scheme, which had been negotiated with the Association, which helped a great deal, but it must be remembered that doctors were not always visiting somebody in an emergency; there were many normal visits. It would be extremely difficult in practice to have a special privileged category of persons.

Strike in Malta

Mr. J. CRONIN (Loughborough, Lab.) asked the Secretary of State for the Colonies on May 5 for a statement on the circumstances of the recent strike of doctors in the Malta Government Service. Mr. MACLEOD stated that the strike arose over the appointment of a new deputy senior medical officer, and the administrative channels for dealing with the affairs of the medical department within the Government Secretariat. The Medical Officers' Union advised the Government on April 30 of its intention to strike as from

midnight the following day, without previously giving any notice of the existence of a dispute. An emergency medical service was operating.

Poliomyelitis and Vaccination

Mrs. JOYCE BUTLER (Wood Green, Lab.) asked the Minister of Health what was the number of cases of poliomyelitis and paralytic poliomyelitis, respectively, in 1958 and in 1959 in the different age groups, and the state of their previous vaccination.

Mr. D. WALKER-SMITH told her on May 2 that the information requested regarding cases of poliomyelitis occurring in 1958 and in 1959 was set out in the following tables:

Year	No. of Cases				
	Paralytic		Non-paralytic		Totals
	Under 15 Years of Age	15 and Over	Under 15 Years of Age	15 and Over	
1958	959	458	428	147	1,992
1959	512	220	215	74	1,021

Year	Cases Reported Among Those who had had two or More Injections of Poliomyelitis Vaccine				
	Paralytic		Non-paralytic		Totals
	Under 15 Years of Age	15 and Over	Under 15 Years of Age	15 and Over	
1958	88	4	83	3	178
1959	76	10	56	14	156

Note: All figures for 1959 are provisional.

She also asked for information about poliomyelitis and paralytic poliomyelitis, respectively, which occurred within 30 days of vaccination in each of the different age groups, in 1958 and in 1959, and was given the following figures:

Year		No. of Cases				
		Paralytic		Non-paralytic		Totals
		Under 15 Years of Age	15 and Over	Under 15 Years of Age	15 and Over	
1958	After 1 dose	36	3	17	0	56
	,, 2 doses	12	0	10	0	22
	,, 3 ,,	3	0	0	0	3
	Totals ..	51	3	27	0	81
1959	After 1 dose	16	6	8	0	30
	,, 2 doses	2	0	3	1	6
	,, 3 ,,	4	1	2	0	7
	Totals ..	22	7	13	1	43

Note: The figures for 1959 are not yet complete.

Universities and Colleges

UNIVERSITY OF OXFORD

Dr. R. G. Tucker has been reappointed University Demonstrator in Biochemistry and Dr. R. S. Creed University Demonstrator in Physiology, both from October 1, 1960, to September 30, 1965. The George Herbert Hunt Travelling Scholarship for 1960 has been awarded to Dr. R. D. Stedeford (Worcester College).

Dr. R. G. Bannister has been elected to a Radcliffe Travelling Fellowship.

UNIVERSITY OF CAMBRIDGE

Dr. P. A. Merton has been reappointed University Lecturer in the Department of Physiology, with tenure from October 1, 1960, to the retiring age.

UNIVERSITY OF GLASGOW

On April 30 the degree of M.D. was conferred, with commendation, on I. A. Porter.

UNIVERSITY OF EDINBURGH

Dr. K. B. Roberts has been appointed Senior Lecturer in the Department of Physiology, and Colonel J. E. C. Robinson part-time Lecturer in the Department of Public Health and Social Medicine.

Dr. Agnes R. Macgregor has resigned from the appointment of Honorary Reader in the Department of Pathology, as from September 30, 1960.

UNIVERSITY OF LONDON

The title of Reader in Chemical Pathology in the University has been conferred on Dr. G. R. Webster in respect of the post held by him at Guy's Hospital Medical School, from January 1, 1960.

The title of Fellow of University College, London, has been conferred on Professor J. F. Danielli, F.R.S., Professor of Zoology and Head of Department, King's College, London; and the title of Honorary Fellow of University College, London, on Sir Simon Marks, Hon.F.R.C.S.

Dr. J. Greenwood Wilson, medical officer of health for the Port and City of London, has been appointed a Fellow of King's College, London.

Mr. R. V. Bradlaw, M.D.S., F.R.C.S., F.D.S., has been appointed a teacher of dental surgery (oral medicine) at the Institute of Dental Surgery.

The University of London will commemorate the tercentenary of the Royal Society and the centenary of the award of the first degrees in science by the University of London on July 22, 1960, when the honorary degree of Doctor of Science will be conferred upon His Majesty King Gustaf VI Adolf of Sweden.

The honorary degree of Doctor of Science will also be conferred on the following Fellows or Foreign Members of the Royal Society on that occasion: Professor Homi Jehangir Bhabha, Director and Professor of Experimental Physics, Tata Institute of Fundamental Research, Bombay; Professor Detlev Wulf Bronk, O.B.E.(Hon.), President of the Rockefeller Institute, and President of the National Academy of Sciences; Sir Macfarlane Burnet, O.M., Director of the Walter and Eliza Hall Institute for Medical Research, Melbourne, and Professor of Experimental Medicine, University of Melbourne; Professor George Charles de Hevesy, Forskning Institute for Organic Chemistry, Sweden; and Sir Thomas Merton, Treasurer of the Royal Society, 1939–56.

Dr. Charles F. Harris has been re-elected Vice-Chancellor from September 1 for the university year 1960–1.

Dr. Michael Shepherd, Senior Lecturer in Psychiatry at the Institute of Psychiatry, has been appointed to the University Readership in Psychiatry tenable at that institute.

UNIVERSITY OF BIRMINGHAM

The honorary degree of D.Sc. will be conferred on Sir Geoffrey Jefferson, F.R.S., Emeritus Professor of Neurosurgery in the University of Manchester, in July.

Dr. D. A. Heath, Lecturer in Pathology, and Dr. B. D. Bower, Lecturer in Paediatrics and Child Health, have been promoted to senior lectureships from October 1, 1960.

Mr. F. C. Walker, F.R.C.S., has been appointed Lecturer in Surgery.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

At a meeting of the faculty held on April 4, with the President, Mr. Arthur Jacobs, in the chair, the following were admitted Fellows of Faculty: *qua Physician*, A. C. Arntzenius, C. C. H. Chew, D. G. Chinniah, J. L. C. Dall, M. G. Dunnigan, A. B. E. S. Ibrahim, J. C. J. Ives, Julia A. Keane, A. L. Linton, S. M. Malik, B. G. S. Murthy, I. H. Randhawa, A. Sinclair, W. D. Smith, R. G. Spector; *qua Surgeon*, W. M. Borthwick, R. J. Scothorne.

At a meeting of the Faculty held on May 2, with the President, Mr. Arthur Jacobs, in the chair, the following were admitted Fellows of Faculty *qua* surgeon: A. K. Bain, D. P.-C. Chan, W. G. Millar.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

The following candidates were successful at the recent examination for the newly established Dublin Diploma in Obstetrics,

awarded by the College: S. Ahmed, B. N. Chakraborty, R. N. Jariwala, S. H. M. Logan, G. F. Mirza, M. L. O'Flaherty, L. C. Patel, T. F. Shaw.

On April 1 the following candidates were duly admitted Licentiates in Medicine and Midwifery, having passed the final examination in medicine, surgery, and midwifery of the Conjoint Board of Ireland: Lesley J. Clements, M. Davy, M. M. Jadwat, Sibertie Kissoon, D. J. O'Brien, Tai Hon Li.

ROYAL COLLEGE OF SURGEONS IN IRELAND

FACULTY OF ANAESTHETISTS

The President, Vice-president, and Council of the Royal College of Surgeons in Ireland have instituted a Faculty of Anaesthetists and have elected the following to the first Board of Faculty: *Dean*, Dr. T. J. Gilmartin; *Vice-Dean*, Dr. V. C. McCormick; Dr. P. Drury Byrne, Dr. F. Nagle, Dr. S. Kenny, Dr. P. Murray, Dr. J. A. Woodcock, Dr. R. Davys, Dr. J. W. Dundee, Dr. S. H. Love. *Council Representative*, Mr. D. J. Riordan; *ex-officio*, Mr. T. G. Wilson, President, and Mr. S. F. Heatley, Vice-President of the Royal College of Surgeons in Ireland.

The Foundation Fellows, whose names will be published at a later date, will be formally admitted to the Faculty by the President on Friday, July 8, 1960, at 5 p.m. The Faculty's first scientific meeting, to be held in the Royal College of Surgeons in Ireland, is being organized for the following day, July 9.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in March was 99, compared with 88 in the previous month and 112 in March, 1959.

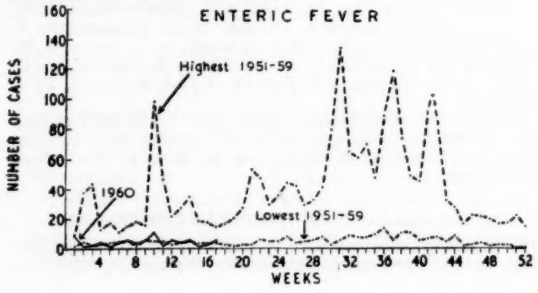
The numbers of cases of industrial diseases in the United Kingdom reported during March were as follows: lead poisoning 1; anthrax 1; epitheliomatous ulceration 17; chrome ulceration 12; total 31. There were no deaths.

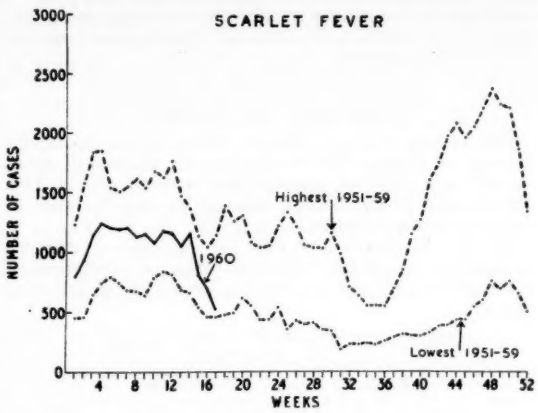
Influenza and Pneumonia

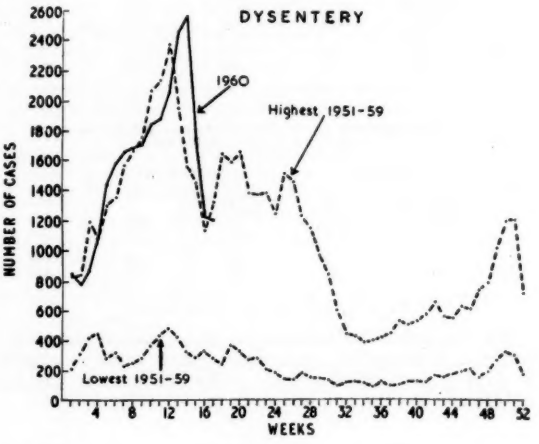
During the early spring the deaths from influenza, bronchitis, and pneumonia in England and Wales were all much fewer in 1960 than in 1959. The influenza deaths have remained low (35 in the week ending April 30); deaths from bronchitis, at around 450, are now about the same as they were a year ago, but deaths from pneumonia are still over the 600 mark. During the week ended April 30 they amounted to 607, compared with 416 during the same week a year ago.

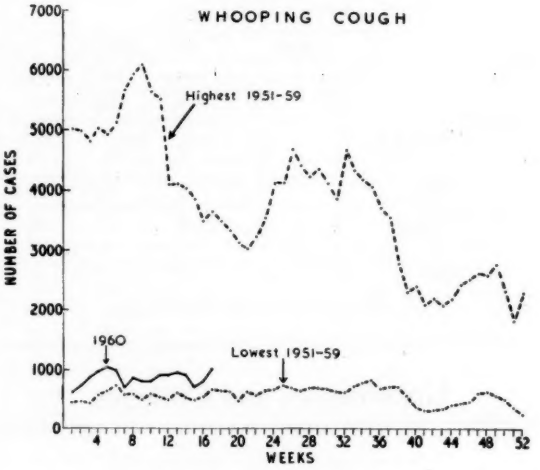
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Road Accidents in 1959

In 1959 5,840 men and women and 680 children were killed on the roads of Britain. More than 80,000 people were seriously injured and about a quarter of a million slightly injured. Approximately 417,000 vehicles were involved—i.e., one-twentieth of the total number on the roads. The killed or injured fell into the following groups: 45,000 drivers, 78,000 motor-cyclists (including scooter and moped riders), 52,000 pedal-cyclists, 67,000 pedestrians, and 40,000 children.

1959 Returns for Scotland

The preliminary summary of the Scottish vital statistics for 1959 gives a birth rate of 19.1 for the year, 0.1 below the rate for 1958. The infant mortality was 28.4 per 1,000 live births, compared with 27.7 in 1958. The death rate was 12.1 per 1,000 population—0.1 above the rate for 1958. Deaths from respiratory tuberculosis numbered 514, 124 fewer than in the previous year, and deaths from other forms of tuberculosis numbered 63, 14 more than in 1958. 634 deaths were attributed to the principal epidemic diseases—583 from influenza, 23 from meningococcal infections, 18 from measles, 8 from whooping-cough, 1 from diphtheria, and 1 from streptococcal sore throat. Only one death was attributed to acute poliomyelitis, compared with 16 in the preceding year. Deaths from violence numbered 2,568 and were 6 more than in 1958. Of these deaths, 441 were ascribed to suicide, 634 to road-transport accidents, 1,088 to home accidents, and 693 to other forms of violence: all these figures are very close to those of 1958.—*Quarterly Return of the Registrar-General, Scotland*, No. 420, 1960, H.M.S.O., Edinburgh.

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending April 23	Week Ending April 30
Dysentery		
Cheshire	46	**54**
Bollington U.D.	3	**15**
Dukinfield M.B.	15	**14**
Stalybridge M.B.	4	**13**
Essex	134	**90**
West Ham C.B.	13	**11**
Chigwell U.D.	16	**21**
Romford M.B.	12	**19**
Gloucestershire	28	**25**
Bristol C.B.	20	**24**
Kent	22	**52**
Chatham M.B.	0	**29**
Lancashire	232	**227**
Liverpool C.B.	16	**38**
Manchester C.B.	18	**18**
Oldham C.B.	20	**13**
Swinton and Pendlebury M.B.	14	**19**
Worsley U.D.	21	**13**
London	151	**162**
Islington	16	**32**
Lewisham	7	**15**
St. Pancras	8	**15**
Southwark	22	**15**
Middlesex	56	**63**
Heston and Isleworth M.B.	3	**12**
Nottinghamshire	37	**24**
Beeston and Stapleford U.D.	4	**11**
Charlton U.D.	17	**11**
Warwickshire	22	**24**
Birmingham C.B.	19	**15**
Yorkshire West Riding	110	**114**
Bradford C.B.	17	**31**
Leeds C.B.	9	**16**
Sheffield C.B.	30	**21**
Glamorganshire	17	**29**
Ogmore and Garw U.D.	11	**18**
Glasgow	165	**124**
Edinburgh	24	**35**
Measles		
Leicestershire	159	**183**
Leicester C.B.	128	**103**
Lancashire	604	**677**
Liverpool C.B.	150	**222**
Yorkshire	169	**201**
Leeds C.B.	65	**75**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 23** (No. 16) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	7	0	2	0		4	1	5	0	2
Dysentery	1,228	151	255	19	1	837	102	152	8	3
Encephalitis, acute	4	0	1	0		1	0		0	
Enteric fever:										
Typhoid	3	0	0	0	1	5	0	0	0	1
Paratyphoid	0	0	0	0	13	4	0	1 (B)	0	
Food-poisoning	130	15	9	0		283	85	12	0	
Infective enteritis or diarrhoea under 2 years				12	19				8	18
Measles*	2,484	96	46	2	31	14,474	695	642	331	236
Meningococcal infection	22	3	1	0		23	3	10	1	1
Ophthalmia neonatorum	23	3	6	0		34	0	6	0	
Pneumonia†	361	7	224	9	3	340	24	197	13	6
Poliomyelitis, acute:										
Paralytic	4	1	0	3	4	10	3	1	1	2
Non-paralytic	2	0	0			11	1	1		
Puerperal fever§	156	33	4	2		223	37	11	0	
Scarlet fever	707	30	12	21	12	769	37	53	31	23
Tuberculosis:										
Respiratory	378	42	68	13		562	59	78	9	
Non-respiratory	57	3	4	6		72	7	9	3	
Whooping-cough	815	55	202	1	27	710	12	64	44	158

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	1	0	1	6	0	1	0	1
Influenza	44	0	1	0	0	58	1	0	4	8
Measles	0	0	0	0	0		0	0	0	0
Meningococcal infection		1	0				0	1		
Pneumonia	613	36	23	5	8	492	38	30	25	19
Poliomyelitis, acute	0	0		0	0	1	0		0	0
Scarlet fever	0	0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	57	3	3	0	2	78	6	5	2	2
Non-respiratory			4	0	1		0	2	0	0
Whooping-cough	0	0	0	0	0	0	0	0	1	0
Deaths 0–1 year	319	34	34	7	11	331	36	35	7	14
Deaths (excluding stillbirths)	10,356	797	654	129	213	9,487	703	593	153	183
LIVE BIRTHS	14,748	1236	1168	304	389	14,815	1280	1100	311	420
STILLBIRTHS	336	20	23			360	26	27		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Nuffield Foundation G.P. Awards

As part of its programme for the advancement of health, the Nuffield Foundation, in co-operation with the College of General Practitioners, is prepared to award to men and women of the United Kingdom:

(1) Three Fellowships (each for a period of six consecutive months) to enable general medical practitioners of outstanding ability, preferably between the ages of 35 and 45, to undertake approved study overseas in July to December, 1961, in some subject of importance to general practice. The value of the Fellowship award will cover for the Fellow (and for his wife) tourist return travel by air and other fares at tourist rates, together with an adequate subsistence allowance. (2) Three Assistantships to enable suitable persons to gain experience as locum tenens in the practices of the Fellowship holders in their absence from the United Kingdom. The value of the Assistantship award will be up to £750 for six months, in addition to travelling expenses.

Details and application forms may be obtained from Mr. L. FARRER-BROWN, Director, The Nuffield Foundation, Nuffield Lodge, Regent's Park, London, N.W.1, to whom applications must be sent by October 31.

Rockefeller Foundation Grants

As part of a European programme for research on cell metabolism the Rockefeller Foundation in the first quarter of the year made a five-year grant of $50,000 to Oxford University, where work is being carried out under Sir HANS KREBS, F.R.S., on the relationship between vitamin B_{12} and the growth factor, folic acid; the control of the specific structure of proteins by nucleic acids; and the primary biological effects of ionizing radiations. During the same period Cambridge University received a $25,000 grant to continue the work conducted there under Dr. T. R. R. MANN, F.R.S., on the biochemical and physiological factors associated with reproduction. These grants are part of the $1,497,350 allocated to the medical and natural sciences out of the Rockefeller Foundation's first-quarter allocation of nearly $5m.

Beit Memorial Fellowships

The trustees of the Beit Memorial Fellowships for medical research have announced that Professor Sir LINDOR BROWN, F.R.S., has been re-elected a member of the advisory board. The following elections have been made:

Junior Fellowships (£900 a year): Mr. D. C. WATTS, M.Sc., at the Department of Biochemistry, University College, London; Dr. J. R. CASLEY-SMITH, at the Sir William Dunn School of Pathology, Oxford; Mr. P. F. FOTTRELL, M.Sc., at the Tissue Culture Laboratory, Biochemistry Department, University of Glasgow; Mr. A. J. ROWE, M.A., at the Department of Colloid Science, Cambridge; Mr. G. F. V. SEAMAN, Ph.D., at the Department of Medicine, Cambridge. *Senior Fellowship* (£1,300 a year): Dr. J. R. TATA, D.Sc., at the National Institute for Medical Research, Mill Hill, London.

"Journal of Reproduction and Fertility"

The new quarterly *Journal of Reproduction and Fertility* has been founded by the Society for the Study of Fertility to replace the annual volumes, *Studies on Fertility*, which have hitherto contained the Society's proceedings and other papers. It will publish original papers, abstracts of proceedings, and occasionally reviews and bibliographies, dealing with the morphology, physiology, biochemistry, and pathology of reproduction in man and animals, and with the biological, medical, and veterinary problems of fertility. The editor is Dr. C. R. AUSTIN, D.Sc. (National Institute of Medical Research, Mill Hill, London, N.W.7), to whom papers should be submitted, and Dr. A. S. PARKES, F.R.S., is chairman of the editorial board. There are corresponding members in Australia, Canada, France, India, Israel, and the United States. The publishers are Blackwell Scientific Publications, Ltd., 24–25, Broad Street, Oxford, to whom subscriptions should be sent (20s. or $3.50 an issue, 70s. or $12 a year, post free).

British Association of Physical Medicine

The seventeenth Annual Meeting of the British Association of Physical Medicine, presided over by Dr. H. BURT, was held at King's College Hospital last month.

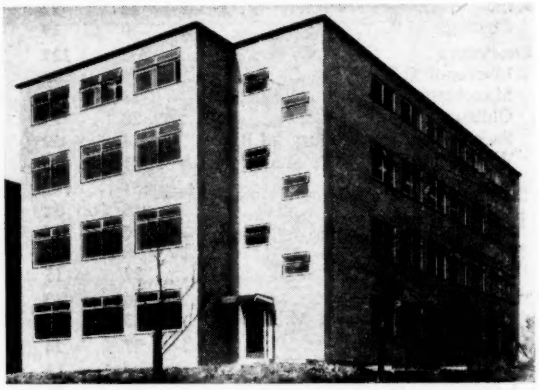
In the scientific programme there was a symposium on the metabolic diseases affecting the locomotor system. The main speakers were Dr. R. M. MASON, Dr. S. MATTINGLY, Dr. J. ANDERSON, and Dr. A. M. RACKOW. Short papers were given on measurements of the conduction rate in the median nerve in patients with the carpal tunnel syndrome before and after treatment; a study of neuroticism in out-patients attending physical medicine departments; the work of a hospital resettlement clinic; the experimental production of osteoporosis in rats with prolonged steroid therapy; the effect of superficial and deep heating on the blood flow of the lower limb; and the use of dexamethasone esters in soft-tissue and intra-articular injections. Dr. F. S. COOKSEY demonstrated the work of the new Functional Assessment Unit at King's College Hospital in which occupational therapists and physiotherapists assess the problems patients are likely to meet at home. The annual dinner of the association was held at the Apothecaries' Hall. Mr. D. WALKER-SMITH, Minister of Health, proposed "The Association."

Ciba Foundation

During 1959 guests at the Ciba Foundation averaged 11 a night—903 visitors, on one or more visits, from 43 different countries. The Foundation's *Report for 1959* also notes as the principal event of the year the Anniversary Symposium on "Significant Trends in Medical Research" under the chairmanship of Sir HAROLD HIMSWORTH, F.R.S.; the first Ciba Foundation symposia to take place outside Great Britain—in Naples, in Paris, and in Buenos Aires; the introduction of the one-day international study groups; and the end of the five-year period of research into the fundamental aspects of ageing.

Wellcome Wing, Birmingham Medical Faculty

The Wellcome Wing of Birmingham University's Clinical Research block, providing accommodation for the departments of medicine and surgery, has recently been completed.



The Wellcome Trust gave £95,000 towards the building, and the scientific equipment has been supplied by the University Grants Committee.

The new wing, shown here, has four stories, the top two being devoted to surgery. The third floor includes laboratories and a seminar room seating 50 people and fitted with projector services and a small library. The operating-theatre on the top floor will comfortably take all the monitoring apparatus necessary for experimental open-heart work, but it would also accommodate up to four tables for simpler work. The sound-proof, plenum-ventilated-and-heated kennel room can house 18 dogs, and there is a special kitchen for the preparation of dog food. There are also two laboratories: one with a fume chamber for isotope work, and a large electronics laboratory which at the moment is particularly concerned with apparatus for open-heart work, cardiac arrest, and Stokes–Adams disease.

Medical Television in America

An American organization, the Council on Medical Television, which held its first meeting last autumn under the auspices of the Institute for Advancement of Medical

Communication, has published a report of the meeting's proceedings. One of the Council's main concerns is the use of television for postgraduate medical education.

Several medical schools apparently use open-circuit T.V. to present continuation courses suitable for the practising physician, and the Council point out that, though there have been few, if any, complaints from lay viewers, many questions remain to be answered: "How broad are the areas in clinical medicine that can be effectively covered without offending public sensibilities or producing iatrogenic effects? Does the lack of overt complaints mean that *no* harm is being done? How many lay viewers watch the programme even though they understand it only partially, if at all?" There is a strong feeling that, although such a system can be used, it is a temporary expedient until private channels are developed. The Council believes that some scientific subjects, such as physiology, biochemistry, and bacteriology, are suitable for programmes viewed simultaneously by both practitioners and laymen.

Hospital Board Appointments

The following are among those reappointed or appointed members of the boards of governors or of the regional hospital boards:

Boards of Governors, Provincial Teaching Hospitals.—United Newcastle Hospitals: Dr. C. N. ARMSTRONG. *United Leeds Hospitals:* Professor A. S. JOHNSTONE, Mr. G. ARMITAGE.* *United Sheffield Hospitals:* Mr. J. C. ANDERSON, Dr. I. B. SNEDDON.* *United Cambridge Hospitals:* Dr. D. G. BRATHERTON,* Dr. A. J. ROOK.* *United Oxford Hospitals:* Dr. L. K. LEDGER, Mr. J. A. STALLWORTHY, Dr. A. R. H. WILLIAMSON, Dr. J. L. BOLDERO,* Dr. H. R. VICKERS.* *United Bristol Hospitals:* Professor R. J. BROCKLEHURST, Professor T. F. HEWER, Mr. C. A. BROWN,* Mr. R. E. HORTON.* *United Cardiff Hospitals:* Mr. H. R. S. HARLEY, Dr. L. H. HOWELLS. *United Birmingham Hospitals:* Dr. W. T. COOKE,* Professor A. B. MACGREGOR.* *United Manchester Hospitals:* Professor W. I. C. MORRIS, Sir HARRY PLATT, Dr. A. MORGAN-JONES.* *United Liverpool Hospitals:* Dr. A. R. D. ADAMS.*

Boards of Governors, London Teaching Hospitals.—St. Bartholomew's Hospital: Dr. C. F. HARRIS, Mr. E. G. TUCKWELL. *London Hospital:* Dr. J. GRAHAM, Dr. G. T. HANKEY, Professor C. F. BARWELL,* Mr. E. C. B. BUTLER,* Dr. L. COMYNS.* *Royal Free Hospital:* Dr. K. G. LLOYD-WILLIAMS, Dr. A. M. C. MACPHERSON, Dr. F. V. GARDNER,* Dr. P. E. THOMPSON HANCOCK.* *University College Hospital:* Sir GEORGE REID MCROBERT. *Middlesex Hospital:* Professor C. A. KEELE, Mr. D. H. PATEY, Dr. F. C. GOLDING,* Mr. W. R. WINTERTON,* Mr. A. J. B. GOLMSMITH.* *Charing Cross Hospital:* Dr. E. GRUNDY, Mr. N. C. TANNER, Mr. A. R. MAKEY.* *St. George's Hospital:* Dr. H. W. GORDON, Dr. J. H. HOVELL,* Mr. W. MCKISSOCK.* *Westminster Hospital:* Mr. E. STANLEY LEE, Professor R. J. V. PULVERTAFT, Dr. J. L. FRANKLIN.* *St. Mary's Hospital:* Mr. A. G. CROSS, Professor A. NEUBERGER, F.R.S., Dr. S. L. SIMPSON, Dr. E. R. WILLIAMS, Dr. G. B. MITCHELL-HEGGS,* Mr. I. G. ROBIN.* *Guy's Hospital:* Sir WILLIAM KELSEY FRY, Mr. G. F. GIBBERD, Mr. R. J. CANN.* *King's College Hospital:* Sir WILFRED P. H. SHELDON, Dr. J. S. S. FAIRLEY.* *St. Thomas's Hospital:* Professor THOMAS POMFRET KILNER, Dr. H. J. WALLACE.* *Hammersmith, West London, and St. Mark's Hospitals:* Professor J. C. MCCLURE BROWNE, Dr. R. COVE-SMITH, Sir ALLEN DALEY, Sir FRANCIS FRASER, Dr. B. C. MORSON.* *Hospital for Sick Children:* Dr. R. E. BONHAM-CARTER, Dr. G. H. NEWNS, Dr. B. SCHLESINGER, Dr. J. A. SCOTT, Mr. D. INNES WILLIAMS. *National Hospitals for Nervous Diseases:* Sir RUSSELL BRAIN, Dr. J. ST. CLAIR ELKINGTON, Dr. M. KREMER. *Royal National Throat, Nose, and Ear Hospital:* Mr. J. C. HOGG, Mr. G. H. HOWELLS, Dr. I. FRIEDMANN.* *Moorfields Eye Hospital:* Mr. C. A. COOK.* *Bethlem Royal and Maudsley Hospitals:* Dr. B. G. C. ACKNER,* Dr. J. R. ELLIS.* *St. John's Hospital for Diseases of the Skin:* Dr. L. FORMAN, Dr. S. C. SHANKS, Dr. J. E. M. WIGLEY.* *Hospitals for Diseases of the Chest:* Sir RUSSELL BROCK, Dr. J. L. LIVINGSTONE, Dr. K. ROBSON, Mr. J. R. BELCHER.* *Royal National Orthopaedic Hospital:* Mr. C. W. MANNING,* Dr. P. G. WALKER.* *National Heart Hospital:* Dr. H. A. BULMAN, Dr. J. M. H. CAMPBELL.* *St. Peter's, St. Paul's, and St. Philip's Hospitals:* Mr. H. G. HANLEY, Mr. A. R. C. HIGHAM. *Royal Marsden Hospital:* Mr. A. H. HUNT.* *Queen Charlotte's and Chelsea Hospitals:* Mr. H. G. E. ARTHURE, Dr. C. NEWMAN. *Eastman Dental Hospital:* Sir WILLIAM KELSEY FRY, Professor ROBERT BRADLAW,* Dr. R. R. STEPHENS.*

Regional Hospital Boards—Newcastle: Dr. C. N. ARMSTRONG, Dr. R. E. JOWETT, Mr. R. S. VENTERS. *Leeds:* Dr. W. A. HYSLOP, Mr. G. WHYTE WATSON. *Sheffield:* Dr. C. S. O'FLYNN, Dr. R. J. DONALDSON,* Professor A. W. KAY.* *East Anglia:* Professor A. L. BANKS. *North-west Metropolitan:* Dr. K. G. LLOYD-WILLIAMS, Professor F. C. WILKINSON, Mr. J. D. S. FLEW.* *North-east Metropolitan:* Dr. T. R. HILL, Dr. J. A. MOODY, Mr. R. W. REID. *South-east Metropolitan:* Sir WILLIAM KELSEY FRY, Dr. V. F. HALL, Dr. L. C. COOK, Mr. J. H. MAYER. *South-west Metropolitan:* Mr. A. L. ABEL, Sir GEOFFREY TODD. *Oxford:* Dr. D. H. G. MACQUAIDE. *South-western:* Professor R. J. BROCKLEHURST, Professor A. V. NEAL, Mr. R. V. COOKE.* *Welsh:* Dr. P. A. TREVOR JONES, Dr. E. WYN JONES, Mr. E. K. ROY THOMAS, Dr. M. G. WILLIAMS. *Birmingham:* Dr. J. H. SHELDON, Sir ARTHUR P. THOMSON. *Manchester:* Dr. R. W. LUXTON,* Dr. M. PARKES, Sir HARRY PLATT, Mr. T. S. HESLOP.* *Liverpool:* Professor A. B. SEMPLE, Professor H. L. SHEEHAN. *Wessex:* Dr. C. H. D. BARTLEY, Dr. L. H. D. THORNTON. (* New members.)

Chelsea Clinical Society

The annual dinner of the Chelsea Clinical Society was held this year in the Apothecaries' Hall, on the walls of which are the ancient banners which decorated the ceremonial barges of the apothecaries on their visits by river to the Physic Garden in Chelsea. The guest of honour, Mr. PETER SCOTT, proposed the toast of the Society. The out-going president, Dr. G. TURNER PITTS, replied and then inducted into office the new president, Sir JOHN PEEL, K.C.V.O.

History of Scientific Ideas Unit

The Nuffield Foundation has formed a Unit for the History of Scientific Ideas under the direction of Dr. STEPHEN TOULMIN, former professor of philosophy at Leeds University. The first aim of the unit, to which £60,000 has been allocated, will be to produce a basic collection of teaching films and textbooks for use in sixth forms and introductory university courses in the history and philosophy of science.

Regional Hospitals' Consultants and Specialists Association

The annual dinner of the Regional Hospitals' Consultants and Specialists Association was held at the House of Commons on April 29. Mr. HAROLD DODD was in the chair, and the speakers included Lord MORAN, Sir JOHN CHARLES, Sir STEPHEN KING-HALL, and Mr. ROBERT COOKE, M.P.

R.S.M.'s Richard Kovacs Prize

The Royal Society of Medicine's Richard Kovacs Prize, value £50, is awarded triennially for distinguished work in physical medicine. Applications should be received by the Honorary Secretary, Section of Physical Medicine, 1, Wimpole Street, London, W.1, by September 30.

Memorial Center Fellowship

The Memorial Center for Cancer and Allied Diseases is offering a one-year Fellowship in Medical Neoplasia from July 1, 1961. Details from Dr. H. D. DIAMOND at the Center, 444, East 68th Street, New York, 21, N.Y., U.S.A.

People in the News

Sir GORDON GORDON-TAYLOR has been awarded a Doctorate of Medicine *honoris causa* by the University of Lille.

Dr. PHOEBUS TUTTNAUER, who is 70 and who started painting five years ago, has a view of Lake Lugano in the Royal Academy's Summer Exhibition.

COMING EVENTS

Society for the Study of Infectious Disease.—Meeting at Ruchill Hospital, Glasgow, May 21, 10.30 a.m., including afternoon session on "Hospital Cross-infection."

Fourth Almroth Wright Lecture.—Dr. P. L. MOLLISON, "The Role of Complement in Blood-group Reactions," May 23. For details see *Journal* advertisement p. 68.

Association of School Medical and Dental Officers of Scotland.—Summer meeting, Largs, Ayrshire, June 4. Visits to Red Cross House (residential care and training for cripples) and Inverclyde House (Scottish Council of Physical Recreation). Details from Dr. MAUD P. MENZIES, Rosmaris, 34, Rhannan Road, Glasgow, S.4.

Charterhouse Rheumatism Clinic. — Gilbert Scott Memorial Lecture: Lord COHEN OF BIRKENHEAD, "The Present Status of Collagen Disease," Barnes Hall, Royal Society of Medicine, June 10, 5 p.m. Open to all members of the medical profession.

Indian Medical Service Dinner Club.—Annual dinner, East India and Sports Club, Ltd., St. James's Square, London, S.W.1, June 10, 7 p.m. Tickets from the secretary, I.M.S. Dinner Club, Medical Department, Commonwealth Relations Office, Matthew Parker Street, London, S.W.1.

1st International Symposium of Underwater Medicine.—Cannes, June 15–19. Details from Dr. J. FERRARI, 10, Place du Commandant Lamy, Cannes (A.-M.), France.

Symposium on Staphylococci.—Under the aegis of the Faculty of Medical Sciences of Buenos Aires. Organizers: Professor J. M. LESTON and Professor C. RECHNIEVSKI. July 14–16. Written contributions invited. Details from Dr. M. E. JÖRG, Corrientes 316, Esc. 153, Buenos Aires, South America.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.*1.

JOURNAL OF CLINICAL PATHOLOGY

The Effect of Heparin on the Early Stages of Blood Coagulation. J. R. O'Brien.
Observations on the Effect of Magnesium on Blood Coagulation. R. G. Huntsman, B. A. L. Hurn, and H. Lehmann.
A Simplification in the Estimation of "Prothrombin Time" for the Control of Anticoagulant Therapy. J. W. Keyser and R. B. Payne.
A Critical Evaluation of Red Cell and Plasma Volume Techniques in Patients with Burns. J. W. L. Davies.
The Development of an Acquired Haemoglobin Abnormality Caused by Thermal Injury. S. Baar.
The Relationship of Serum Gamma-globulin Concentration to Malaria and Sickling. J. C. Edozien, A. E. Boyo, and D. C. Morley.
Thrombotic Thrombocytopenic Purpura. B. Bornstein, J. H. Boss, J. Casper, and M. Behar.
Stress Zones in Foetal Arteries. J. H. Robertson.
The Identification of a Fluorescent Reducing Substance in the Urine of Patients with Rheumatoid Arthritis. Mary McMillan.
Factors Affecting the Uptake of Lissamine Green by Serum Proteins. C. J. Brackenridge.
A Rapid and Precise Method for the Determination of Urea. J. K. Fawcett and J. E. Scott.
A Simple and Rapid Method for the Simultaneous Determination of Calcium and Magnesium from the Same Sample of Blood Serum. G. S. Kovács and K. E. Tárnoky.
A Simple Method for the Determination of Serum Haptoglobins. J. A. Owen, F. C. Better, and J. Hoban.
Infection with Different Species of Leptospires in Husband and Wife. M. S. Pathy.
The Coliene Typing of Coliform Bacilli in the Study of Cross-infection in Urology. K. B. Linton.
Technical Methods:
A Technique of Blood pH Estimation. E. G. Hardy.
A Capillary Tube Method of Rh Typing Using Albumin Agglutinating Anti-D Serum. A. Lawrence.
A Modified Quick's One-stage Test for the Control of Out-patients on Anticoagulant Therapy. B. A. Thompson.
A Manometric Micro-apparatus for Estimating Oxygen. F. Rappaport, F. Eichhorn, and M. Nutman.
An Orbital Shaker. K. W. Keohane and W. K. Metcalf.
Seventh European Congress of Haematology.
Book Reviews.

Volume 15, No. 2. (Bi-monthly; £4 4s. annually.)

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 16

DENTAL AND MEDICAL SOCIETY FOR THE STUDY OF HYPNOSIS.—At Royal Society of Medicine, 8 p.m., annual general meeting.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor C. H. Stuart-Harris: Virus Infections of the Respiratory Tract.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School.—5 p.m., Third Almroth Wright Lecture by Professor R. R. Porter, Ph.D.: Structure of Gamma Globulin and Antibodies.

Tuesday, May 17

ILFORD MEDICAL SOCIETY.—At King George Hospital, Ilford, 8.45 p.m., annual general meeting and cocktail party.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., Dr. T. F. Corkhill (New Zealand): Slight Disproportion as the Critical Factor in Prolonged Labour.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Dr. R. R. Willcox: Vaginitis Caused by Trichomonas and Candida Infestation.
SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Bolingbroke Lecture by Sir Eric Riches: Carcinoma of the Bladder.

Wednesday, May 18

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: The Haemopoietic System in Skin Diseases.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. S. Plummer: Bronchopulmonary Mycetomas.
ROYAL FREE HOSPITAL, Gray's Inn Road, London, W.C.—5.15 p.m., Dr. Alfred Gellhorn (Columbia University, New York): Some Medical Aspects of Cancer.
WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine, 8.30 p.m., Sir Eric Riches: Carcinoma of the Bladder.

Thursday, May 19

BRITISH INSTITUTE OF RADIOLOGY.—At Reid-Knox Hall, 32, Welbeck Street, W., 7.30 p.m., annual general meeting. 8 p.m., 39th Silvanus Thompson Memorial Lecture by Dr. V. E. Cosslett, Ph.D., F.Inst.P.: X-ray Microscopy—Retrospect and Prospect.
HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Dr. H. W. C. Griffiths: Crush Injuries of the Chest.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Dr. J. A. Gorsky: An Historical Inquest and Exhumation.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor C. H. Stuart-Harris: Virus Infections of the Respiratory Tract.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At Manson House, 26, Portland Place, W., 7.30 p.m., Dr. G. S. Nelson: Schistosomes as Zoonoses in Africa. A discussion will follow.
ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Physiology Department, Queen's College, Small's Wynd, Dundee, 5 p.m., Professor Thomas McKeown: Human Prenatal Growth.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration by Sir Paul Mallinson: Psychiatry.

Friday, May 20

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4.30 p.m., Skinner Lecture by Professor J. Frimann-Dahl (Oslo): Tumours of the Pancreas.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. S. Pegum: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. J. L. Livingstone.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professor F. C. Ormerod: New Concepts of the Function of the Cochlear and Vestibule.
INSTITUTE OF NEUROLOGY.—4.30 p.m., Dr. Denis Williams: Syndromes of the Basilar Artery.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. Ian Orr: Selection of Operation for Peptic Ulcer.

Saturday, May 21

●CAMBRIDGE UNIVERSITY POSTGRADUATE MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, symposium on Anaesthesia for Patients with Circulatory Disease. *Morning session:* 10.30 a.m., Dr. H. A. Fleming: Clinical Examination of the Cardiovascular System; 11.45 a.m., Dr. D. W. Barkham: The Electrocardiogram—Its Use Preoperatively. *Afternoon session:* 2.30 p.m., Mr. R. Wright: Anaesthesia for Patients with Cardiovascular Disease (Excluding Cardiac Operations); 3.30 p.m., Mr. J. P. Payne: The Action of Anaesthetic and Allied Drugs on the Heart.
NORTH-WESTERN THORACIC SOCIETY.—At Cheshire Joint Sanatorium, Market Drayton, 11 a.m., joint meeting with Midland Thoracic Society.
YORKSHIRE SOCIETY OF ANAESTHETISTS.—At Huddersfield Royal Infirmary, 10.45 a.m., Mr. W. N. B. George, A.R.I.B.A.: Planning of the New General Hospital at Huddersfield; 11.45 a.m., Dr. C. S. Ward and Dr. A. R. Kerr: Old Age in Everyday Anaesthesia; 2.30 p.m., Dr. G. Jackson Rees: Some Aspects of Paediatric Anaesthesia.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Green.—On April 5, 1960, at the Women's Hospital, Wolverhampton, Staffs, to Maureen, wife of William C. Green, M.B., B.Ch., a brother for Michael and Beverley—Geoffrey Kevin.
Starck.—On May 6, 1960, at Perivale Maternity Hospital, to Pauline and Gordon Starck, a son—Andrew Philip.
Trigg.—On April 28, 1960, at the Weir Maternity Hospital, Balham, London, S.W., to Sylvia J. Jordan, M.B., B.S., wife of Kenneth H. Trigg, M.B., B.S., D.Obst.R.C.O.G., a sister for Jennifer and Hilary—Cecilia Jane.

DEATHS

Elt.—On April 28, 1960, at Summer Lane, Wirksworth, Derby, Edward Ernest Elt, M.R.C.S., L.R.C.P., late of London, N., and St. Jean, Cap Ferrat, France.
Fletcher.—On April 20, 1960, Rowe Brennand Fletcher, M.D., of Green Knott, Windermere, Westmorland.
Friend.—On April 24, 1960, at St. Albans City Hospital, Francis Friend, M.D., D.M.R.E., of St. Albans, Herts, formerly of Edgware, Middx.
Hogg.—On April 27, 1960, at Foresterhill, Aberdeen, William James Hogg, M.D., D.P.H., of Forest Hill, Stonehaven, Kincardineshire.
Hunt.—On April 19, 1960, Henry Hunt, L.R.C.P.&S.I. & L.M., surgeon captain, R.N., retired, aged 90.
Hunter.—On April 27, 1960, at 65, Pentland Terrace, Edinburgh, Alexander Hunter, *M.C.*, M.B., Ch.B., late of Moseley, Birmingham, Warwicks.
Kirkwood.—On April 26, 1960, at his home, Lawbrook, Gomshall, Surrey, William Douglas Kirkwood, M.D., aged 74.
Monie.—On April 29, 1960, at Westfield, Alexander Street, Lanarks., James Monie, M.B., Ch.B.
Rogerson.—On April 30, 1960, William Albert Rogerson, M.R.C.S., L.R.C.P., of Little Saling, Essex, formerly of Bexley Heath, Kent, aged 67.
Sinclair.—On April 23, 1960, at Avimore, Camberley, Surrey, George Hulseberg Sinclair, M.B., F.R.C.S.Ed., aged 88.
Walsh.—On April 21, 1960, Michael Anthony Walsh, L.R.C.P.&S.I. & L.M., D.P.M., late of Tooting Bec, London, S.W.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Maternal Jaundice and the Foetus

Q.—*Is there likely to be any damage to the foetus from maternal jaundice occurring during the first few weeks of pregnancy? Is it known whether maternal jaundice at any stage of pregnancy can cause kernicterus?*

A.—This question raises many issues on which information is lacking or uncertain, and the problem is complicated by the fact that any effect on the foetus may vary with the cause of the maternal jaundice. After making limited inquiries I have been unable to find any reported case of kernicterus resulting from maternal jaundice of any kind. The possibility could arise only when indirect (unconjugated) bilirubin is in circulation, and it is not known for certain whether this type of bilirubin can cross the placental barrier.[1] That it cannot is rather supported by the fact that certain writers[2] say that the baby delivered from a mother suffering from virus hepatitis is never jaundiced at birth.

Even if indirect bilirubin can cross from mother to foetus it is unlikely to cause kernicterus, because in jaundice in adults the serum bilirubin level rarely if ever approaches the figure above which damage to the basal nuclei of the foetus becomes a real risk. It may be added that other factors, as yet unsettled, may be necessary to the development of kernicterus: for example, pigments other than bilirubin may be involved.

Jaundice caused by virus hepatitis and by acute liver failure in pregnancy can affect the foetus adversely in other ways. The associated toxaemia or viraemia (rather than the jaundice) can kill the foetus, to cause abortion or stillbirth. Most obstetricians have seen intrauterine death of the foetus under such circumstances. Even if the foetus is not killed it is likely to be born prematurely. It may be added that there are reliable accounts of maternal virus hepatitis being transmitted to the foetus *in utero*, to manifest itself in the usual way after birth.

When the mother acquires virus hepatitis in the early weeks of pregnancy, then, assuming that abortion does not result, it is natural to wonder whether it can cause malformation of the foetus—as does the viraemia of rubella. The statistical evidence so far available indicates that this is not a real risk.[3]

Allen and Diamond[4] and Thorling[5] also give further information and a bibliography on the various matters raised here.

REFERENCES

1 Sherlock, Sheila, *Diseases of the Liver and Biliary System*, 2nd ed., 1958. Blackwell, Oxford and London.
2 Cattan, R., and Cattan, A., *Rev. int. Hépat.*, 1959, **9**, 399.
3 Jeffcoate, T. N. A., *Brit. med. J.*, 1960, **2**, 581.
4 Allen, P. H., and Diamond, L. K., *Erythroblastosis Fetalis*, 1958. J. and A. Churchill Ltd., London.
5 Thorling, L., *Acta med. scand.*, 1955, **151**, *Suppl.* 302.

Malignancy in Uterine Polypi

Q.—*Does malignancy occur in cervical and uterine polypi?*

A.—Certain carcinomas, sarcomas, and mesodermal mixed tumours of the uterus, both cervical and corporeal, assume a polypoidal form. These are malignant from the outset. Although their histological features generally make their nature clear, their malignant character is sometimes overlooked. Thus clinical recurrence of what is at first regarded as an innocent cervix polyp may first draw attention to the fact that the lesion is a mesodermal mixed tumour of a malignant nature.

It is more difficult to be certain whether innocent adenomatous polypi of the endometrium and endocervix can, after a time, become malignant. The general view is that this occurrence, although possible, is rare. It may be added that the presence of an innocent polyp at the external os may coincide with the existence of a malignant lesion at a higher level in the uterus. This second lesion can be overlooked if the polyp is avulsed without simultaneous curettage.

Risk of Angiography

Q.—*What are the risks of submitting a man of 38 who has completely recovered from a subarachnoid haemorrhage to carotid angiography and possibly surgical intervention compared with the risk of leaving things alone?*

A.—The most important criterion in assessing the need for an investigation is the influence the result may have on a course of action. If it makes no difference, the investigation should probably not be carried out. The question therefore resolves into the need for surgical treatment. In considering this, the morbidity and mortality of the operation have to be set against that of the disease.[1 2 3] The indications for operation vary with the situation and size of the aneurysm, and when this is known they have to be assessed separately. Up to about two months from the haemorrhage angiography should be performed. Beyond this period it is not desirable to perform angiography on a symptomless patient who shows no localizing signs. The chances of further haemorrhage decrease as time passes, and are fairly small after six months; at this stage the operative risk is greater. Angiography itself carries a morbidity, but the degree is difficult to determine. It is probably higher in the first few days after haemorrhage than later. The contrast substance is rapidly removed from the brain and circulation, though minor, but normally reversible, changes in capillaries may occur. When the above criteria are used the risk of angiography is always less than that of the disease or operation, for when the operative risk exceeds that of the disease angiography is not recommended.

REFERENCES

1 Ask-Upmark, E., and Ingvar, D., *Acta med. scand.*, 1950, **138**, 15.
2 Hyland, H. H., *Arch. Neurol. Psychiat. (Chicago)*, 1950, **63**, 61.
3 Walton, J. N., *Canad. med. Ass. J.*, 1955, **72**, 165.

Rhythm of Growth

Q.—*Birds' feathers are said to grow in jerks. Is this a general law of nature, and in particular do human capillaries, growing, say, in granulomatous tissue when they bud from the arches, grow in jumps?*

A.—To use the word "jerk" for the growth of birds' feathers is misleading; they grow with a *diurnal* rhythm. Similar diurnal phases are recognizable in cell division in the epithelial cells of the skin. What physiological or biochemical rhythm is responsible for these phasic changes is unknown, though many such diurnal alternations have been identified—sleep being perhaps the most obvious one. There is no evidence that blood capillaries in granulation tissue grow with any phasic regularity; it would require careful analysis of cinematograph records to disclose any rhythm, were there one.

Food Value of Mangoes

Q.—*What is the food value and vitamin content of Indian mango? Does its vitamin content vary with ripeness, when it is dried, or when it is preserved in syrup or oil, or pickled in vinegar?*

A.—Ripe mangoes (*Mangifera indica*) contain up to 1% of protein, 14% of carbohydrate, a trace of fat, and about 85% of water. They therefore provide only about 60 calories per 100 g. They are rich in ascorbic acid, with 30 mg. per 100 g. as a typical value, and in carotene, with up to 5,000 i.u. per 100 g. A portion of mango of 4 oz. (113 g.) will therefore go far towards satisfying the daily requirements for vitamins A and C. Ripe mangoes contain only small amounts of B vitamins and of calcium and iron.

Unripe green mangoes contain much less vitamin C and carotene, and somewhat less carbohydrate, than are found in the ripe fruit, but they are considerably richer in iron.[1 2]

No information is readily available about the effects of preservation on the nutritive value of mangoes. From general considerations, however, we might expect that drying would lead to heavy losses of vitamin C and to smaller losses of carotene. Much would depend on the temperature during drying and on the time of storage afterwards. Carotene should suffer only slight losses in mangoes preserved in syrup or oil, and the losses in ascorbic acid ought to be less than after drying. Acid media, such as vinegar, are reputed to favour the preservation of ascorbic acid, but might promote the destruction of carotene.

REFERENCES

1 *The Nutritive Value of Indian Foods and the Planning of Satisfactory Diets*, 1956, Health Bulletin No. 23. Indian Council of Medical Research.

2 *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, 1945, No. 253.

Interrupted Immunization

Q.—*Patients do not always return for further injections after the first or second of a course of tetanus immunization. What is the state of immunity in these cases? Should a further, full course be given?*

A.—It is generally accepted that a person must be considered non-immune (or incompletely immunized) to tetanus after (1) he has received only one injection of tetanus toxoid, or (2) more than six months have elapsed after two injections of toxoid. Antitoxin would then be needed in the event of injury. Adequate protection can be assumed only after three properly spaced injections.

When there is any departure from the accepted immunization course it is difficult to make general recommendations for completion of immunization after different time intervals. When a person has had only the first injection of a course, and less than three months have elapsed since the injection, the course may be proceeded with in the usual way—namely, the second injection at once and the third injection in six to twelve months' time. If more than three months have elapsed since the first injection of toxoid, a new full course of three injections should be given.

If a person has had only two of the three injections, and less than a year has elapsed since the second injection, the third injection could be given to complete the primary course. If one to five years have elapsed, two doses of toxoid should be given, spaced six weeks apart. If more than five years have elapsed, a new full course of three injections should be commenced.

Immune persons who are wounded are given 1 ml. of tetanus toxoid intramuscularly: antitoxin is not required. In order that the immune status may be maintained, reinforcement is indicated after five years.

Various other aspects of the prevention of tetanus in injured persons, involving passive and active immunization, are discussed by Parish, Laurent, and Moynihan.[1]

REFERENCE

1 Parish, H. J., Laurent, L. J. M., and Moynihan, N. H., *Brit. med. J.*, 1957, **1**, 639 and 1063.

NOTES AND COMMENTS

Nail-biting.—Dr. DAPHNE SASIENI (Hadleigh, Essex) writes: Does the question ("Any Questions?" April 2, p. 1069) mean that all other treatments have failed, therefore should hypnosis be tried? I should like to suggest to the questioner that he tackles the problem in this way, concentrating on the nail-biting aspect only. Tell the girl that lots of people who have bitten their nails for years eventually learn to stop doing so, but that it is not easy and will take several months. Tell her to get a nail-brush, a sandpaper nail-file, and a pair of sharp-pointed scissors and to scrub her nails every evening and to snip off any bits of skin or cuticle obviously torn and ragged. Then to rub her finger along a bitten nail to feel how rough it is, and, having felt the roughness, let her sandpaper off the rough pieces: this is difficult, and, if the nail has been badly bitten, may be slightly painful. Tell her to try and smooth all her nails in all directions every day, and then explain to her that it is impossible to bite a smooth nail, since there is nothing for her teeth to get hold of. The difficulty is initially to get a smooth surface. Then—and this is most important—tell the girl not to expect to be able to give up biting ten nails at once—no one can—but let her make a pact with herself to stop biting one nail for one week. The others will be difficult to bite, since they will be kept smooth, but tell her that if the chosen one comes anywhere near her mouth she is to take it out (no one but herself knows which nail has been chosen). Then the next week a nail from the other hand should be chosen, and an extra nail should be added each week. As the nails begin to grow they should be kept smooth with the file. Long nails should not be grown at this stage because they will break, and having broken will be bitten. Ten good nails should not be expected at the end of ten weeks—six or seven in that time would be satisfactory. The girl should be told that if she has bitten a nail again by accident she should not be depressed or annoyed with herself: she should merely smooth off the rough bits and let the nail grow again. During the second three months the nails may be allowed to grow a little longer. If the patient has always bitten her nails when she is "worked up" before examinations, etc., she should not be disappointed if she finds herself biting some of her nails at these times. The treatment will soon get over the problem. After a few months, when the girl has achieved presentable hands, she will probably have gained considerably in personality and confidence.

OUR EXPERT replies: The suggested treatment could succeed only if the girl's motivation to stop nail-biting were much stronger than her unconscious need for relief from tension or the emotional satisfaction found in the continuing habit. In any case, no adolescent could carry through the régime proposed without very strong adult support—kindly, and completely uncritical. The original question about using hypnosis suggests that either the girl herself is in a state of acute anxiety about the habit or that her parents are. If it is the former, then help is needed not only with breaking the habit but also with the excessive anxiety attached to what is, after all, a fairly innocuous habit. If it is the latter, the parents will not be able to be truly supportive and uncritical when the steady progression of the "cure" is interrupted. Therefore, outside help is needed. The suggested régime might well prove highly successful if the doctor proposing it first formed a therapeutic relationship with the girl, after satisfying himself or herself that the underlying cause of the symptom would not be aggravated by the removal of the symptom.

Corrections.—The structural formula of guanethidine shown in "To-day's Drugs" (April 30, page 1359) should have contained an 8-membered ring instead of the 6-membered ring.

In the annotation on the new Poisons Rules (May 7, p. 1418) the abbreviated summary of the instructions regarding repeated dispensing of Schedule 4A and 4B prescriptions may have been misleading. According to the Rules the number of times a prescription is to be repeated or the intervals at which it may be dispensed must be stated. If the number of repeats is not given but the interval between repeats is, then the prescription may be dispensed three times in all. On the other hand, if the intervals between repeats are not stated but the number of times the prescription may be repeated is, the prescription may not be dispensed more often than once every three days.

In the *Journal* of April 30, p. 1375, the sum of £125,000 said to have been given to the Royal College of Obstetricians and Gynaecologists by the Nuffield Provincial Hospitals Trust was made up of £75,000 given by Lord Nuffield himself and £50,000 given by the Trust.

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